PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 47/02, 31/70 // (A61K 31/70, 31:52, 31:505)

A1

(11) International Publication Number: **WO 99/55372**

(43) International Publication Date: 4 November 1999 (04.11.99)

(21) International Application Number: PCT/EP99/02794

(22) International Filing Date: 26 April 1999 (26.04.99)

(30) Priority Data:
9809213.3 29 April 1998 (29.04.98) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CURRIE, Robin [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). JAIN, Sunil [IN/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). WOOD, Allen, Wayne [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US).

(74) Agent: CRAWLEY, Karen; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: HOMOGENEOUS PHARMACEUTICAL COMPOSITIONS COMPRISING ABACAVIR, LAMIVUDINE AND ZIDOVUDINE

(57) Abstract

A pharmaceutical composition comprising a homogeneous combination of abacavir, lamivudine, and zidovudine in an amount which achieves antiviral efficacy, a process for the preparation of such a composition, and a method of inhibiting human immunodeficiency virus (HIV) which comprises administering such a composition to an HIV infected patient is disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

HOMOGENEOUS PHARMACEUTICAL COMPOSITIONS COMPRISING ABACAVIR, LAMIVUDINE AND ZIDOVUDINE

The present Invention relates to novel pharmaceutical compositions combining the agents abacavir, lamivudine and zidovudine into a single homogenous dosage form, useful in the treatment of diseases in mammals, including humans.

Abacavir (also known as (1S, 4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, 1592U89) and its antiviral use, particularly against HIV infections is described in European Patent Specification Number 0434450. The succinate salt of (1S, 4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol is described in WO96/06844. The hemisulfate salt of (1S, 4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol is described in WO98/52949. Abacavir is currently under clinical investigation as an anti-HIV pharmaceutical agent.

Lamivudine (also known as EPIVIR™, 3TC™, (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one, (-)-cis-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine) has proven antiviral activity against human immunodeficiency virus (HIV) and other viruses such as hepatitis B. Lamivudine and its use against HIV are described in EP 0382526 and WO91/17159. Crystalline forms of lamivudine are described in WO92/21676. Combinations of lamivudine with other reverse transcriptase inhibitors, in particular zidovudine, are described in WO92/20344.

Zidovudine (also known as 3'-azido-3'-deoxythymidine, RETROVIR™) for the treatment of HIV and other viruses. Zidovudine is further described in United States Patent Nos. 4,818,538, 4,828,838, 4,724,232, 4,833,130 and 4,837,208, all of which are incorporated herein by reference.

The synergistic effect of the combination of abacavir, lamivudine and zidovudine is described in WO96/30025. However, there is no indication in this document of how to achieve homogeneity of the three active ingredients when formulating as a single tablet.

The success of modern multiple-drug treatments for HIV often requires strict compliance with a complex treatment regimen that can require the administration of many different drugs per day, administered at precisely timed intervals with careful attention to diet. Patient non-compliance is a well known problem accompanying such complex treatment regimens. See Goodman & Gilman, The Pharmacological Basis of Therapeutics, 9th ed., pp. 1704-1705 (1996). 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 multiple active ingredients into a single tablet. However, simply combining the three drugs into a single tablet would result in a tablet size too large to swallow without difficulty. Furthermore, the greater the amount of drug in the formulation, the more excipients are needed in order to compress the mixture into a tablet. Increased amounts of some excipients can have adverse effects on tablet properties and can lead to problems of, for example, dissolution, content uniformity, hardness, and segregation.

Segregation is a major concern when attempting to formulate a single homogenous tablet containing multiple active ingredients having different densities and different particle sizes. Segregation of active ingredients in pharmaceutical powders and granulations is a widely recognised problem that can result in inconsistent dispersions of the active ingredients in final dosage forms. Some of the main factors contributing to segregation are particle size, shape and density. Previous attempts to formulate tablets containing multiple drugs were hindered by precisely such segregation problems. Although mixed blends were initially homogeneous, the active ingredients segregated during material handling and prior to tablet compression.

Glidants are substances that have traditionally been used to improve the flow characteristics of granulations and powders by reducing interparticulate friction. See Lieberman, Lachman, & Schwartz, Pharmaceutical Dosage Forms: Tablets, Volume 1, p. 177-178 (1989), incorporated herein by reference. Glidants are typically added to pharmaceutical compositions immediately prior to tablet compression to facilitate the flow of granular material into the die cavities of

tablet presses. Glidants include colloidal silicon dioxide, asbestos free talc, sodium aluminosilicate, calcium silicate, powdered cellulose, microcrystalline cellulose, corn starch, sodium benzoate, calcium carbonate, magnesium carbonate, metallic stearates, calcium stearate, magnesium stearate, zinc stearate, stearowet C, starch, starch 1500, magnesium lauryl sulfate, and magnesium oxide.

Research into the problem of segregation in pharmaceutical compositions has surprisingly demonstrated that glidants can be used to increase and aid blend composition homogeneity. The novel compositions of the present Invention use glidants to effect and maintain homogeneity of active ingredients during handling prior to tablet compression.

It is therefore an object of the present Invention to provide a pharmaceutical composition comprising the active ingredients abacavir, lamivudine and zidovudine, or pharmaceutically acceptable derivatives thereof, in a sufficiently homogenised form, and a method for using this pharmaceutical composition.

A further object of the present invention is to provide a pharmaceutical composition in the form of a tablet with high drug loading, while maintaining favorable tablet properties and suitable tablet size.

A further object of the present Invention is to utilise glidants to reduce the segregation of active ingredients in pharmaceutical compositions during pre-compression material handling.

A still further object of the present Invention is to provide pharmaceutical compositions which combine the active ingredients abacavir, lamivudine and zidovudine, or pharmaceutically acceptable derivatives thereof, with a pharmaceutically acceptable glidant, resulting in a mixture characterised by a pharmaceutically acceptable measure of homogeneity.

Another object of the present Invention is to provide a pharmaceutical composition comprising abacavir, or a pharmaceutically acceptable derivative thereof, lamivudine, or a pharmaceutically acceptable derivative thereof, and

zidovudine, or a pharmaceutically acceptable derivative thereof, together with one or more pharmaceutically acceptable carriers and optionally, other therapeutic and/or prophylactic ingredients. Other therapeutic agents may include agents that are effective for the treatment of viral infections or associated conditions such as (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514], oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine), acyclic nucleosides (e.g. acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir), acyclic nucleoside phosphonates (e.g. (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC) or PMEA, ribonucleotide reductase inhibitors such as 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl) thiocarbonohydrazone, 3'azido-3'-deoxythymidine, other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-didehydrothymidine, protease inhibitors such as indinavir, ritonavir, nelfinavir, [3S-[3R*(1R*, 2S*)]]-[3[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-tetrahydro-3-furanyl ester (141W94), oxathiolane nucleoside analogues such as cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, ribavirin, 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), tat inhibitors such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-(H)one (Ro5-3335), 7-chloro-1,3-dihydro-5-(1H-pyrrol-2yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429), interferons such as α-interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole; pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof, or non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine (BI-RG-587), loviride (α -APA) and delavuridine (BHAP), and phosphonoformic acid, and 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266), and quinoxaline NNRTIs such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293), hydroxyurea, or inhibitors of inosine monophosphate dehydrogenase, such as mycophenolic acid or esters thereof.

The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Still another object of the present Invention is to simplify treatment regimens for HIV and other viruses with the goal of enhancing patient compliance by providing a simplified dosage form containing pharmaceutically acceptable amounts of abacavir, lamivudine and zidovudine or pharmaceutically acceptable derivatives thereof.

In a first aspect, the present Invention features a pharmaceutical composition, comprising:

i) a safe and therapeutically effective amount of abacavir or a pharmaceutically acceptable derivative thereof;

ii a safe and therapeutically effective amount of lamivudine or a pharmaceutically acceptable derivative thereof;

iii) a safe and therapeutically effective amount of zidovudine or a pharmaceutically acceptable derivative thereof; and

iv) a pharmaceutically acceptable glidant

characterised in that the active ingredients are homogenous.

In a further aspect, the present invention features a pharmaceutical composition comprising abacavir, or a pharmaceutically acceptable derivative thereof, lamivudine, or a pharmaceutically acceptable derivative thereof, and zidovudine, or a pharmaceutically acceptable derivative thereof in an amount from about 30% to about 70% of total composition weight. The pharmaceutical composition may advantageously be in the form of a tablet, said tablet having 30% to 60% drug loading, advantageously 40% to 60% drug loading.

The phrase "safe and 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 without severely harming the tissues of the mammal to which the drug or pharmaceutical agent is administered.

The phrase "pharmaceutically acceptable derivative," as used herein, means any pharmaceutically acceptable salt, solvate, ester, or salt of such ester, or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) the intended active ingredient or any active metabolite or residue thereof.

The phrase "pharmaceutically acceptable derivative of abacavir" as used herein, means any pharmaceutically acceptable salt, solvate, ester, or salt of such ester, ofabacavir, or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) abacavir or any antivirally active metabolite or residue thereof.

The phrase "pharmaceutically acceptable derivative of lamivudine" as used herein, means any pharmaceutically acceptable salt, solvate, ester, or salt of such ester, of lamivudine, or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) lamivudine or any antivirally active metabolite or residue thereof.

The phrase "pharmaceutically acceptable derivative of zidovudine" as used herein means any pharmaceutically acceptable salt, solvate, ester, or salt of such ester, of zidovudine, or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) zidovudine or any antivirally active metabolite or residue thereof.

The phrase "homogenous" as used herein, means that the active ingredients are substantially evenly dispersed throughout the part of the finished tablet which comprises them (for example, in the case of a film coated compression tablet, the active ingredients are evenly dispersed throughout the tablet core). The homogeneity of active ingredients in a tablet may be ascertained by means of the drug uniformity measure.

The phrase "safe and effective amount," as used herein, means that amount of an agent that is required to perform the function being sought by the researcher or clinician without severely harming the tissues of the mammal to which the agent is administered.

The phrase "drug loading," as used herein, means the ratio of drug to total weight of tablet.

Preferably, lamivudine is provided substantially free of the corresponding (+)-enantiomer. "Substantially free" as used herein, means that there is less than about 10% w/w of the (+)-enantiomer present compared with the amount of lamivudine. Preferably there is less than about 5% w/w of the (+)-enantiomer present compared with the amount of lamivudine.

In a further aspect, the present invention provides a method for treating, reversing, reducing or inhibiting retroviral infections in particular HIV infections, in a mammal, in particular a human, which method comprises administering to said mammal a safe and effective amount of a composition according to the invention.

In a further aspect, the present invention provides the combined use of abacavir, or a pharmaceutically acceptable derivative thereof, lamivudine, or a pharmaceutically acceptable derivative thereof, zidovudine, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable glidant in the manufacture of a medicament for the treatment of a retroviral infection, in particular an HIV infection.

It will be appreciated by those skilled in the art that reference herein to "treatment" extends to both the prophylaxis and the treatment of an established malady, infection or its symptoms.

The compositions of the present Invention employ a safe and therapeutically effective amounts of (-)-(1S, 4R) -4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir) or a pharmaceutically acceptable derivative thereof, 3'-azido-3'-deoxythymidine (zidovudine) or a pharmaceutically acceptable derivative thereof, and (-)-cis-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (lamivudine) or a pharmaceutically acceptable derivative thereof, along with a safe and effective amount of a pharmaceutically acceptable glidant to maintain the compositions homogeneity prior to tablet compression. Typically

the particle size and shape of the three active ingredients will be different. The pharmaceutical formulation is homogenous in the sense that the active ingredients are substantially evenly dispersed throughout that part of the finished formulation which includes abacavir, lamivudine, zidovudine and the glidant. For example, in the case of a film coated compression tablet, the active ingredients are evenly dispersed through the tablet core.

Abacavir may be prepared by the method described in European Patent Specification Number 0434450 or WO95/21161, which are incorporated herein by reference hereto. The succinate salt of 1592U89 may be prepared by the method described in WO96/06844, which is incorporated herein by reference hereto. The hemisulfate salt of 1592U89 may be prepared by the method described in WO98/52949, which is incorporated herein by reference hereto. Preferred salts of abacavir include the succinate salt and the hemisulfate salt.

Methods for the preparation of lamivudine are described in, inter alia, WO 92/20669 and WO 95/29174 both incorporated herein by reference.

Methods for the preparation of zidovudine are described in United States. Patent No. 5,011,829, incorporated herein by reference.

The compositions of the present invention may optionally employ a safe and effective amount of a diluent, a safe and effective amount of a disintegrant, and a safe and effective amount of a lubricant or any other safe and effective amounts of excipients commonly used in the art.

The compositions of the present invention may include from 0 to about 2% magnesium stearate; from about 0.05 to about 5% glidant; from 0 to about 5% sodium starch glycollate; and from about 20 to about 50% microcrystalline cellulose.

Glidants are substances which have traditionally been used to improve the flow characteristics of granulations and powders by reducing interparticulate friction. See, Remington, The Science & Practice of Pharmacy, p. 1619, 19th ed. (1995) and see Lieberman, Lachman, & Schwartz, Pharmaceutical Dosage Forms:

Tablets, Volume 1, p. 177-178 (1989), both of which are incorporated herein by reference. Improving flow characteristics helps to reduce tablet press clogging and malfunction and minimises tablet weight variation. Glidants are typically added to pharmaceutical compositions just prior to tablet compression to facilitate the flow of granular material into the die cavities of tablet presses. Silicon dioxide (SiO_2), also referred to as colloidal silica, fumed silicon dioxide, fumed silica, light anhydrous silicic acid, or silicic anhydride may be used in the compositions of the present invention. Silicon dioxide is sold under the tradenames AEROSIL™ and CAB-O-SIL™. Other glidants that may be used in the compositions of the present invention include asbestos free talc, sodium aluminosilicate, calcium silicate, powdered cellulose, microcrystalline cellulose, corn starch, sodium benzoate, calcium carbonate, magnesium carbonate, metallic stearates, calcium stearate, magnesium stearate, zinc stearate, stearowet C, starch, starch 1500, magnesium lauryl sulfate, magnesium oxide, colloidal silicon dioxide in combination with microcrystalline cellulose or ProSolve ™.

The ability of glidants to improve flow characteristics depends on:

(i) their chemical characteristics in relation to the chemical characteristics of the other ingredients of the composition, and;

(ii) physical characteristics such as the size, shape, and distribution, of the glidants and the other components of the granulation or powder composition, as well as the moisture content and temperature of the composition.

Investigation into the problem of active ingredient segregation in pharmaceutical compositions, powders and granulates has led the present Inventors to the surprising discovery that glidants may be used to reduce segregation of active ingredients and thus improve the homogeneity of pharmaceutical compositions, powders and granulates. The present Invention employs from 0.05% to about 5.0% glidant. Below about 0.05% the homogeneity may not be sufficient and with amounts greater that 5.0% no additional homogeneity is gained.

Silicon dioxide may be a preferred glidant because it is relatively inert. A preferred form of silicon dioxide may be fumed colloidal silicon dioxide, which is submicroscopic fumed silica. It is a light, non-gritty amorphous powder.

Particularly about 0.05% to about 1.0% colloidal silicon dioxide is used because below about 0.05% the homogeneity may not be sufficient and with amounts greater that 1.0% no additional homogeneity is gained. Magnesium stearate may be a preferred glidant.

Where glidants are used to improve flow characteristics, they are typically added to the composition immediately prior to compression during the lubrication step. See, Remington, The Science & Practice of Pharmacy, p. 1619, 19th ed. (1995), incorporated herein by reference. However, the present Invention makes use of glidants in the initial mixture to improve and maintain homogeneity during handling prior to compression. A further glidant may be added to the composition immediately prior to compression during the lubrication step in order to improve the flow characteristics of the composition according to the art of pharmaceutical formulation.

The Invention is preferably presented as a pharmaceutical formulation suitable for oral administration. Such formulations may conveniently be presented as discrete units such as tablets, caplets, capsules, or any other form suitable for oral administration and compatible with the compositions of the present Invention, each containing a predetermined amount of the active ingredients. A particularly suitable formulation may be prepared from direct compression or granulation processes. Such formulations may contain safe and effective amounts of conventional excipients such as binding agents, fillers, lubricants, or disintegrants. The tablets may also be coated according to any method known to persons skilled in the art that would not interfere with the tablets' release properties, or the other physical or chemical characteristics of the present Invention. Tablet coating is further described and delineated by Remington, The Science & Practice of Pharmacy 19th ed. 1995 incorporated herein by reference. When desired, the above formulations may also be modified by any method known to persons skilled in the art to achieve sustained release of active ingredients. The formulations may also include a safe and effective amount of other active ingredients, such as antimicrobial agents or preservatives.

These compositions of the present Invention are suitable for administration to humans or other mammals particularly via an oral route of administration.

However, other routes as utilised by medical practitioners and others skilled in the art of pharmaceutical dosage administration such as Pharmacists and Nurses are not foreclosed. One such method would be the crushing of a solid dosage form, mixing with a suitable administration vehicle and administering rectally as an enema. Other routes of administration might include topical and inhalation.

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.

In general, however, a suitable dose of abacavir for administration to a human for treatment of an HIV injection may be in the range of 0.1 to 120 mg per kilogram body weight of the recipient per day, preferably in the range of 3 to 90 mg per kilogram body weight per day and most preferably in the range 5 to 60 mg per kilogram body weight per day.

The current recommended oral dose of lamivudine for adults and adolescents is 150mg twice daily administered in combination with zidovudine. For adults with low body weights (less than 50 kg or 110 lb.) the current recommended oral dose of lamivudine is 2mg/kg twice daily administered in combination with zidovudine. The recommended oral dose of lamivudine in paediatric patients 3 months to 12 years of age is 4mg/kg twice daily, up to a maximum of 150mg twice daily administered in combination with zidovudine.

In general, the current recommended oral dose of zidovudine is 600mg per day in divided doses in combination with other antiretroviral agents. The recommended oral dose in paediatric patents 3 months to 12 years of age is 180mg/m^2 every 6 hours or 720mg/m^2 per day not to exceed 200mg every 6 hours.

Compositions of the present Invention enable patients greater freedom from multiple dosage medication regimens and ease the needed diligence required in

remembering complex daily dosing times and schedules. By combining abacavir, lamivudine and zidovudine into a single dosage form, the desired daily doses may be presented in a single dose or as divided doses, particularly as divided doses, administered at appropriate intervals, for example as two, three, four or more sub-doses per day, particularly as two sub-doses per day.

The compositions of the present Invention conveniently allow administration of three separate compounds in unit dosage form containing, for example, from about 15 to about 1200 mg of abacavir, particularly from about 100 to about 600 mg of abacavir, and most particularly about 350 mg of abacavir, from about 15 to about 1000 mg of lamivudine, particularly from about 100 to about 500 mg of lamivudine and most particularly 150 mg of lamivudine, and from about 30 to 1000 mg of zidovudine, particularly from about 200mg to about 500 mg zidovudine and most particularly 300 mg of zidovudine per unit dosage form.

The composition 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 safe and therapeutically effective amount of abacavir, or a pharmaceutically acceptable derivative thereof; a safe and therapeutically effective amount of lamivudine, or a pharmaceutically acceptable derivative thereof; a safe and therapeutically effective amount of zidovudine, or a pharmaceutically acceptable derivative thereof and a safe and effective amount of a pharmaceutically acceptable glidant.

Any of the various methods known by persons skilled in the art for packaging tablets, caplets, or other solid dosage forms suitable for oral administration, that will not degrade the components of the present Invention, are suitable for use in packaging. Tablets, caplets, or other solid dosage forms suitable for oral administration, may be packaged and contained in various packaging materials particularly glass and plastic bottles and also including unit dose blister packaging. 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 utilised 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 compositions of the present Invention can be formulated using methods and techniques suitable for the compositions physical and chemical characteristics and that are commonly employed by persons skilled in the art in preparing oral dosage forms utilising direct compression or granulation processes. Remington, The Science & Practice of Pharmacy, p. 1615-1623, 1625-1648, and other applicable sections, 19th ed. (1995).

Compositions of the present Invention in their method aspect are administered to a human or other mammal in a safe and effective amount as described herein. These safe and effective amounts will vary according to the type and size of mammal being treated and the desired results of the treatment.

EXAMPLES

The following examples further describe and demonstrate 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.

Example 1

Preparation of (1S, 4R)-cis-4-[2-Amino-6-cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol hemisulfate salt

A stirred mixture of water (25 ml) and isopropanol (IPA) (100 ml) was heated to 45 to 55°C and (1S, 4R)-cis-4-[2-amino-6-cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol succinate salt (WO 96/06844) (50 g)) was added, and washed in with IPA (12.5 ml). The mixture was heated under reflux for about 0.5 h to give a clear solution and then cooled to 65 to 75°C and a solution of concentrated sulfuric acid (6.07 g) in water (12.5 ml) was added. A mixture of IPA (37.5 ml) and water (12.5 ml) was added and the solution was cooled to 45 to 55°C, whereupon a seed of authentic (1S, 4R)-cis-4-[2-amino-6-cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol hemisulfate salt was added. After stirring in this temperature range for about 1h to allow crystallisation to become established, further IPA (300 mL) was added, maintaining the temperature of the mixture in the range 45 to 55°C. The suspension was cooled to 0 to 5°C over about 2h, and the product was filtered, washed with IPA (2 x 75 ml), and dried in vacuo at 40 to 45°C to give the title compound as a fawn coloured powder (34.3 g, 90%); m.p. 224 - 225°C (decomp.); 1H-NMR (DMSO-d6)δ: 10.76(br m, 1, purine NH), 8.53(vbr m, 1, NH), 7.80(s,1,purine CH), 6.67(br m, 1, NH2), 6.13(m,1, = CH), 5.87(m,1, = CH), 5.40(m,1,NCH), 3.45(d, J = 5.8HZ,2, OCH2), 2.96(br, m, 1 CH of cyclopropyl), 2.87(m, 1, CH), 2.67 - 2.57 (M, 1, CH), 1.65 - 1.55(m, 1, CH), 0.84-0.64(m, 4, 2 x CH2 of cyclopropyl).

Example 2

Direct Compression Formulation for the Triple Combination Tablet Containing Abacavir, Lamivudine, and Zidovudine

Component	Quantity (mg)	Percent
Abacavir Hemisulfate	351.0*	26.0
Zidovudine	300.0	22.2
Lamivudine	150.0	11.1
Microcrystalline cellulose	466.9	34.6
Sodium Starch Glycolate, NF	64.5	4.8
Colloidal Silicon Dioxide, NF	4.07	0.3
Magnesium Stearate, NF	13.6	1.0
Total Tablet Weight	1350.0	

* Equilvalent to 300 mg Abacavir free base

Bulk Preparation Method

The quantities of the present example of manufacturing procedure are based on a typical batch size of 400 kg and may be adjusted depending on batch size.

First, the components are weighed from bulk containers in the following amounts:

Ingredients	Amount (kg)
abacavir hemisulfate	104.0
zidovudine	88.88
lamivudine	44.44
microcrystalline cellulose NF	145.48
sodium starch glycolate NF	12.00
colloidal silicon dioxide NF	1.20
magnesium stearate	4.00

The components are then sieved using a Russell-SIV equipped with 14 mesh (1.4mm opening) or an equivalent sieve and mesh, and deposited into a stainless-steel blending container.

The abacavir, zidovudine, lamivudine, microcrystalline cellulose NF, sodium starch glycolate NF, and colloidal silicon dioxide NF are blended for 20 minutes using a suitable blender, such as a Matcon-Buls bin-type blender, a V-blender or

equivalent. The magnesium stearate is then added to the mixture and blending is continued for approximately 2 minutes.

The lubricated blend is then compressed using a suitable rotary tablet press, typically a Courtoy R-190, R-200 or equivalent. In-process controls for tablet weight and hardness are applied at appropriate intervals throughout the compression run and adjustments to the tablet press are made as necessary.

Example 3

Wet Granulation Formulation for the Triple Combination Tablet Containing Abacavir, Lamivudine, and Zidovudine

Component	Quantity (mg)	Percent
Abacavir Hemisulfate	351.0*	34.0
Zidovudine	300.0	29.0
Lamivudine	150.0	14.5
Colloidal Silicon Dioxide, NF	3.1	0.3
Microcrystalline cellulose, NF	160.0	15.5
Povidone, USP	32.0	3.1
Sodium Starch Glycolate, NF	32.0	3.1
Magnesium Stearate, NF	8.0	0.8
Purified Water, USP	q.s.	
Total Tablet Weight	1036.1	

* Equilvalent to 300 mg Abacavir free base

Preparation Method

The components are weighed and sieved using a Russell –SIV equipped with 30 mesh or an equivalent sieve and mesh, and deposited into a stainless-steel blending container.

The abacavir, zidovudine, microcrystalline cellulose, sodium starch glycolate and colloidal silicon dioxide are blended for 1-5 minutes using a suitable granulator/blender, such as Spectrum SP or Fielder PMA or equivalent. A 10-20%w/w Povidone solution in water is prepared and added to granulate the

powder. Additional water may be added during granulation if required. The granules are dried using microwave drying in the granulator such as Spectrum SP or equivalent or dried using a fluid bed dryer such as UniGlatt or Aeromatic MP or Aeromatic Stea-1 or equivalent. The dried granules are milled using a Comill or Fitzmill or equivalent. Lamivudine is added to the milled granules and blended for 15 minutes using a suitable blender, such as Matcon-Buls bin-type blender, a V-blender or equivalent. The magnesium stearate is then added to the mixture and blending is continued for approximately 2 minutes.

The lubricated blend is then compressed using a suitable rotary press, typically a Manesty Beta or Fette or Courtoy or equivalent. In-process controls for tablet weight and hardness are applied at appropriate intervals throughout the compression run and adjustments to the tablet press are made as necessary.

Example 4

Direct Compression Formulation for the Triple Combination Tablet Containing Abacavir, Lamivudine, and Zidovudine

Components and Composition of Abacavir/Lamivudine/Zidovudine Tablets

Component	**Grade (USP/NF)**	**Theoretical Quantity / Dosage Unit (mg)**	**% W/W**
Abacavir Sulfate	Glaxo Wellcome	351.00[1]	26.0
Lamivudine	Glaxo Wellcome	150.00	11.1
Zidovudine	Glaxo Wellcome	300.00	22.2
Microcrystalline Cellulose	NF	464.25	34.4
Sodium Starch Glycolate	NF	64.50	4.8
Magnesium Stearate	NF	20.25	1.5
Total Core Tablet Weight		**1350.00**	100%
Opadry® Green 03B11434	Glaxo Wellcome	29.70	2.2% Target
Purified Water[2]	USP	q.s.	

Note:

[1] Equivalent to 300mg Abacavir per tablet based on a 1.17 factor.

[2] Removed during processing.

Preparation Method

First, the components are weighed from bulk containers and then sieved using a Russell-SIV equipped with 14 mesh (1.4mm opening) or an equivalent sieve and mesh, and deposited into a stainless-steel blending container.

The abacavir, zidovudine, lamivudine, microcrystalline cellulose NF, and sodium starch glycolate NF are blended for 20 minutes using a suitable blender, such as a Matcon-Buls bin-type blender, a V-blender or equivalent. The magnesium stearate is then added to the mixture and blending is continued for approximately 2 minutes.

The lubricated blend is then compressed using a suitable rotary tablet press, typically a Courtoy R-190, R-200 or equivalent. In-process controls for tablet weight and hardness are applied at appropriate intervals throughout the compression run and adjustments to the tablet press are made as necessary.

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims.

Claims

1. A pharmaceutical composition comprising:

i) a safe and therapeutically effective amount of abacavir or a pharmaceutically acceptable derivative thereof;
ii) a safe and therapeutically effective amount of lamivudine or a pharmaceutically acceptable derivative thereof;
iii) a safe and therapeutically effective amount of zidovudine or a pharmaceutically acceptable derivative thereof; and
iv) a pharmaceutically acceptable glidant.

2. A pharmaceutical composition according to Claim 1, wherein the pharmaceutically acceptable glidant is selected from a group consisting of: silicon dioxide, colloidal silicon dioxide, fumed silicon dioxide, calcium silicate, corn starch, magnesium carbonate, asbestos free talc, metallic stearates, calcium stearate, magnesium stearate, zinc stearate, stearowet C, starch, starch 1500, magnesium lauryl sulfate, or magnesium oxide.

3. A pharmaceutical composition according to Claim 2 wherein the pharmaceutically acceptable glidant is fumed silicon dioxide, colloidal silicon dioxide, or fumed colloidal silicon dioxide.

4. A pharmaceutical composition according to Claim 2 wherein the pharmaceutically acceptable glidant is magnesium stearate.

5. A pharmaceutical composition comprising abacavir, or a pharmaceutically acceptable derivative thereof, lamivudine, or a pharmaceutically acceptable derivative thereof, and zidovudine, or a pharmaceutically acceptable derivative thereof, wherein said abacavir, lamivudine and zidovudine are present in an amount of 30% to 70% of total composition weight.

6. The pharmaceutical composition according to any one of Claims 1 to 5 wherein the amount of abacavir is from about 15 to about 1200 mg per unit dosage form.

7. The pharmaceutical composition according to any one of Claims 1 to 5 wherein the amount of lamivudine is from about 15 to about 1500 mg per unit dosage form.

8. The pharmaceutical composition according to Claim 7 wherein the amount of lamivudine is from about 100 to about 500 mg per unit dosage form.

9. The pharmaceutical composition according to Claim 8 wherein the amount of lamivudine is 150mg per unit dosage form.

10. The pharmaceutical composition according to any one of Claims 1 to 9 wherein the amount of zidovudine is from about 30 to about 1000 mg per unit dosage form.

11. The pharmaceutical composition according to Claim 10 wherein the amount of zidovudine is from about 200 to about 500 mg per unit dosage form.

12. The pharmaceutical composition according to Claim 11 wherein the amount of zidovudine is 300 mg per unit dosage form.

13. 1The pharmaceutical composition according to any one of Claims 1 to 12 wherein lamivudine is provided substantially free of the corresponding (+)-enantiomer.

14. The pharmaceutical composition according to any one of Claims 1 to 12 wherein lamivudine is provided such that the corresponding (+)-enantiomer is present in an amount of not more than about 5% w/w of the amount of lamivudine.

15. The pharmaceutical composition according to any one of Claims 1 to 14 wherein the pharmaceutically acceptable glidant is present in an amount of 0.05% to about 5.0% by weight.

16. A pharmaceutical composition according to any one of Claims 1 to 15 wherein the composition is coated with a pharmaceutically acceptable coating.

17. A method for increasing and maintaining the homogeneity of a pharmaceutical composition by including a safe and effective amount of a pharmaceutically acceptable glidant.

18. The method according to claim 17 for increasing and maintaining the homogeneity of a pharmaceutical composition by including a safe and effective amount of a pharmaceutically acceptable glidant, wherein the glidant is selected from the group consisting of: silicon dioxide, colloidal silicon dioxide, fumed silicon dioxide, sodium aluminosilicate, calcium silicate, powdered cellulose, microcrystalline cellulose, corn starch, sodium benzoate, calcium carbonate, magnesium carbonate, asbestos free talc, metallic stearates, calcium stearate, magnesium stearate, zinc stearate, stearowet C, starch, starch 1500, magnesium lauryl sulfate, or magnesium oxide.

19. The method according to Claim 18 for increasing and maintaining the homogeneity of a pharmaceutical composition by including a safe and effective amount of a pharmaceutically acceptable glidant, wherein the glidant is selected from the group consisting of: fumed silicon dioxide, colloidal silicon dioxide, or fumed colloidal silicon dioxide.

20. A method for treating, reversing, reducing or inhibiting retroviral infections by administering a safe and effective amount of a composition according to any one of Claims 1 to 16.

21. The method for treating, reversing, reducing or inhibiting retroviral infections according to Claim 20, wherein the retrovirus is an immunodeficiency virus, including HIV.

22. The use of abacavir or a pharmaceutically acceptable derivative thereof, lamivudine or a pharmaceutically acceptable derivative thereof, zidovudine or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable glidant in the manufacture of a medicament of the treatment of a retroviral infection.

23. An article of manufacture comprising:

i) packaging material; and
ii) a pharmaceutical composition contained within the packaging material, comprising:

a) a safe and therapeutically effective amount of abacavir or a pharmaceutically acceptable derivative thereof;
b) a safe and therapeutically effective amount of lamivudine or a pharmaceutically acceptable derivative thereof;
c) a safe and therapeutically effective amount of zidovudine or a pharmaceutically acceptable derivative thereof; and
d) a pharmaceutically acceptable glidant
wherein the active ingredients are homogenously dispersed throughout the pharmaceutical composition.

24. An article of manufacture according to Claim 23 additionally comprising a brochure containing product information.

25. An article of manufacture according to Claim 23 or Claim 24 wherein the packaging material is unit dose blister packaging.

26. A process for the preparation of a pharmaceutical composition as claimed in any of claims 1-16 which process comprises admixture of abacavir or a pharmaceutically acceptable derivative thereof, lamivudine or a pharmaceutically acceptable derivative thereof, zidovudine or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable glidant.

27. A process as claimed in claim 26, characterised in that the pharmaceutically acceptable glidant is included in the first admixture stage of composition preparation.