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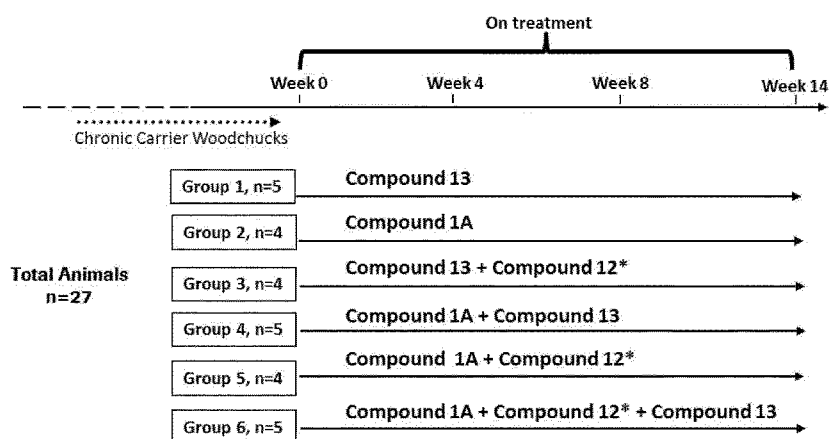
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(54) Title: COMBINATION THERAPY OF AN HBsAg INHIBITOR, A NUCLEOS(T)IDE ANALOGUE AND AN INTERFERON

## Combination therapy of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon



\* Compound 12 administration: three times per week (TIW) for week 0 to 2, no treatment for week 2 to 4, and two times per week (BID) for week 6 to 14.

Figure 1

(57) Abstract: The present invention is directed to compositions and methods for treating hepatitis B virus infection. In particular, the present invention is directed to a combination therapy comprising administration of an HBs Ag inhibitor, a nucleos(t)ide analogue and an interferon for use in the treatment or prophylaxis of chronic Hepatitis B virus infections.



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## Combination therapy of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon

The present invention is directed to compositions and methods for treating hepatitis B virus infection. In particular, the present invention is directed to a combination therapy comprising administration of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon for use in the treatment or prophylaxis of chronic Hepatitis B virus infections.

### 5 FIELD OF THE INVENTION

Chronic infection of Hepatitis B virus (HBV) is a serious public health problem worldwide, with more than 240 million people chronically infected worldwide. HBV belongs to the Hepadnaviridae family of viruses. Following entry into hepatocyte, its viral genome is delivered into nucleus where a covalently closed circular DNA (cccDNA) is formed through  
10 DNA repair of partially double-stranded viral genome. cccDNA serves as the template for transcription of viral RNAs. Viral pre-genomic RNA interacts with other two viral components, capsid protein and polymerase to form capsid particles where viral DNA replication occurs. HBV has an icosahedral core comprising of 240 copies of the capsid (or core) protein. The predominant biological function of capsid protein is to act as a structural protein to encapsidate  
15 pre-genomic RNA and form immature capsid particles in the cytoplasm. This step is prerequisite for viral DNA replication. When a near full-length relaxed circular DNA is formed through reverse-transcription of viral pregenomic RNA, an immature capsid becomes a mature capsid. Most copies of the encapsidated genome efficiently associate with cellular lipids and viral envelope proteins (S, M, and L) for virion assembly and secretion. However, non-infectious  
20 particles are also produced that greatly outnumber the infectious virions. These empty, enveloped particles are referred to as subviral particles (SVPs). The S, M, and L envelope proteins are expressed from a single ORF (open reading frame) that contains three different start codons. All three proteins share a 226aa sequence, the S-domain, at their C-termini. S-domain contains the HBsAg epitope (Lambert, C. & R. Prange. *Virol J*, 2007, 4, 45).

25 Viral proteins expressed from the HBV genome include HBsAg, HBV polymerase, HBV X protein and core protein, and are involved in the multiple steps of the viral life cycle. Many observations showed that several HBV viral proteins could counteract the initial host cellular response by interfering with the viral recognition signaling system. Among these, the excessive

secretion of HBV empty subviral particles may participate to the maintenance of the immunological tolerant state observed in chronically infected patients (CHB). HBsAg, as well as other HBV antigens, may also play a role in suppressing host innate immune responses. The persistent exposure to HBsAg and other viral antigens can lead to HBV-specific T-cell deletion or to progressive functional impairment (Kondo *et al. Journal of Immunology* 1993, 150, 4659–4671; Kondo *et al. Journal of Medical Virology* 2004, 74, 425–433; Fiscicaro *et al. Gastroenterology*, 2010, 138, 682-93;). Moreover HBsAg has been reported to suppress the function of immune cells such as monocytes, dendritic cells (DCs) and natural killer (NK) cells by direct interaction (Op den Brouw *et al. Immunology*, 2009b, 126, 280-9; Woltman *et al. PLoS One*, 2011, 6, e15324; Shi *et al. J Viral Hepat.* 2012, 19, e26-33; Kondo *et al. ISRN Gastroenterology*, 2013, Article ID 935295). Therefore, targeting HBsAg together with HBV DNA levels in CHB patients may significantly improve CHB patient immune reactivation and remission (Wieland, S. F. & F. V. Chisari. *J Virol*, (2005), 79, 9369-80; Kumar *et al. J Virol*, (2011), 85, 987-95; Woltman *et al. PLoS One*, (2011), 6, e15324; Op den Brouw *et al. Immunology*, (2009b), 126, 280-9).

One of the first-line treatments for hepatitis B is IFN- $\alpha$  (interferon alpha), albeit it is limited by its poor, long-term response, and side effects. IFN- $\alpha$ , as a front-line host defense against viral infections, is known to induce interferon-stimulated genes (ISGs), which play a diverse and pleiotropic role in targeting various viral functions at different steps of viral replication cycle, thereby potently suppressing viral infection. In addition, IFN- $\alpha$  has an immunomodulatory effect that can indirectly inhibit HBV replication by affecting cell-mediated immunity in vivo (Micco L., *et al.*, *J. Hepatol*, 2013, 58, 225-233). Even though IFN-administration has shown to inhibit HBV replication in vitro and in vivo (Christen V., *et al.*, *J. Virol.* 2007, 81:159–165; Guan S.H., *et al.*, *J. Gastroenterol*, 2007, 13:228–235; Wieland S.F., *et al.*, *J. Virol.*, 2000, 74, 4165–4173), a large number of individuals, particularly those displaying high viral loads, respond poorly, suggesting that HBV may have evolved mechanisms to antagonize the IFN response, as eluded earlier. Chronic HBV infection is generally characterized by dysfunctional innate and adaptive immune responses (Boni C., *J. Virol.*, 2007, 81, 4215–4225). For example, in HBV infected chimpanzees, IFN- $\alpha$ , was not induced (Wieland S., *et al.*, *Proc. Natl. Acad. Sci. U S A*, 2004, 101, 6669–6674). When treated with Pegylated IFN- $\alpha$ , the effectiveness of a sustained virological response was achieved in only about 30% of HBeAg-positive and 40% of HBeAg-negative cases in clinical studies (Perrillo R., *Hepatology*, 2009, 49, S103-111; Janssen H.L., *et al.*, *Lancet*, 2005, 365, 123-129; Lau G.K., *et al.*, *N. Engl. J. Med.*,

2005, 352, 2682-2695). The antiviral mechanisms of the interferon alpha and the reasons for the differential therapeutic response among the treated patients remain to be elucidated.

Current HBV therapies also include nucleos(t)ide analogues (e.g. Lamivudine, Adefovir, Tenofovir, Telbivudine and Entecavir), which target viral polymerase by inhibiting HBV  
5 polymerase reverse transcription activities. This leads to a decreased viral load and an abolishment of HBV progeny production, but cccDNAs remain intact, and syntheses of all viral proteins and RNAs, and HBsAg level are not affected in the infected hepatocytes. Even with prolonged therapy, nucleos(t)ide analogues have demonstrated very low rates of HBsAg clearance comparable to those observed naturally (Janssen *et al. Lancet*, 2005, 365, 123-9;  
10 Marcellin *et al. N. Engl. J. Med.*, 2004, 351, 1206-17; Buster *et al. Hepatology*, 2007, 46, 388-94).

On the other hand, several novel chemical series such as pyridazones and triazinones derivatives (WO2016/023877), dihydroquinolizinones derivatives (WO 2015/113990, WO 2015/173164, WO/2016/071215 and WO 2016/128335), and tetrahydropyridopyrimidines and  
15 tetrahydropyridopyridines derivatives (WO2016/107832) have been discovered to have the ability to inhibit HBsAg. Unlike current therapies, HBsAg inhibitors inhibit HBV DNA and expression of viral proteins (including HBsAg) by specifically reducing HBV mRNAs.

The Hepatitis B virus (HBV) infection remains a major health problem worldwide which concerns an estimated 240 million chronic carriers who have a higher risk of liver cirrhosis and  
20 hepatocellular carcinoma. Hence, there is certainly an unmet medical need for treatments with improved success rate of inducing HBsAg loss, and/or HBeAg loss, and/ or HBV-DNA reduction, and/or HBV clearance and/or seroconversion, and/or normalization of ALT, and/ or promoting the production of anti-HBs to address the Hepatitis B virus (HBV) infections.

## **SUMMARY OF THE INVENTION**

25 The present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon, in a pharmaceutically acceptable carrier for the treatment or prophylaxis of HBV infection.

In one embodiment, the "HBsAg inhibitor" is a compound of formula (I), (II) or any one of the compounds disclosed in patent application WO 2015/113990 and WO2016/071215,  
30 particularly the "HBsAg inhibitor" herein is (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-10-methoxy-6-

isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In one embodiment, the “interferon” herein is selected from the group consisting of interferon alpha, peginterferon-alpha 2a, recombinant interferon alpha-2a, interferon alpha-2a, peginterferon alpha-2b, recombinant interferon alpha-2b, interferon alpha-2b, glycosylated interferon alpha-2b, interferon alpha-2b XL, recombinant interferon alpha-2c, interferon alpha-2c, interferon beta, peginterferon beta-1a, interferon beta-1a, interferon delta, peginterferon lambda-1, interferon lambda, interferon omega, interferon tau, gamma interferon, interferon alfacon-1, interferon alpha-nl, interferon alpha-n3, albinterferon alpha-2b, BLX-883 (Biolex Inc. and OctoPlus), DA-3021 (Dong-A Pharmaceutical), PEG-Infergen (InterMune Inc. and Inhale Therapeutic Systems), Belerofon (Nautilus Biotech) and wIFN. In one embodiment, the interferon is a y-branched pegylated recombinant human interferon alpha-2b injection Pai Ge Bin (Amoytop Biotech). In one embodiment, the interferon is a non-conjugated interferon alfa or a pegylated alfa-type interferon; particularly the interferon is Roferon A<sup>®</sup> (Hoffmann-La Roche, Inc.), Intron A<sup>®</sup> (Schering-Plough Corp.), Pegasys<sup>®</sup> (Hoffmann-La Roche, Inc.), PegIntron<sup>®</sup> (Schering Corp.) or wIFN; more particularly the interferon is Pegasys<sup>®</sup> or wIFN.

In one embodiment, the “nucleos(t)ide analogue” is any nucleoside and nucleotide analogue known to those skilled in the art. In a further embodiment, the “nucleos(t)ide analogue”

is Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, Clevudine, Tenofovir disoproxil and Tenofovir disoproxil fumarate. Particularly the “nucleos(t)ide analogue” is Entecavir.

### **BRIEF DESCRIPTION OF THE FIGURE(S)**

Fig. 1: Study design of the woodchuck drug combination study. WHV-infected woodchucks were treated with Compound 1A, Compound 12 and Compound 13 alone or in combination for 14 weeks, and then monitored for another 10 weeks without treatment.

Fig. 2: Effect of Compound 1A, Compound 12 and Compound 13 alone or in combination on WHsAg in WHV-infected woodchucks. Shown are mean values and error bars represent the standard error of the mean (SEM). Dashed line shows the lower limit of detection (LLOD) at 30 ng/ml.

Fig. 3: Observed effect (circles) and predicted additive effect (triangles) of the triple combination of Compound 1A, Compound 12 and Compound 13 on WHsAg in WHV-infected woodchucks. Additivity effect of triple drug combination was predicted using the Bliss independence model. Error bars represent the 95% confidence intervals.

### **DETAILED DESCRIPTION OF THE INVENTION**

#### **DEFINITIONS**

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

As used herein, the term “C<sub>1-6</sub>alkyl” refers to a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms. In particular embodiments, C<sub>1-6</sub>alkyl has 1 to 6 carbon atoms, and in more particular embodiments 1 to 4 carbon atoms. Examples of C<sub>1-6</sub>alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl or *tert*-butyl.

As used herein, the term “halo” or “halogen” are used interchangeably herein and refer to fluoro, chloro, bromo, or iodo. Halogen is particularly fluorine, chlorine or bromine.

As used herein, the term “C<sub>1-6</sub>alkoxy” refers to a group of C<sub>1-6</sub>alkyl-O-, wherein the “C<sub>1-6</sub>alkyl” is as defined above; for example methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, 2-butoxy, *tert*-butoxy and the like. Particular “C<sub>1-6</sub>alkoxy” groups are methoxy and ethoxy and more particularly methoxy.

As used herein, the term “C<sub>3-7</sub>cycloalkyl” refers to a saturated carbon ring containing from 3 to 7 carbon atoms, particularly from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Particular “C<sub>3-7</sub>cycloalkyl” groups are cyclopropyl, cyclopentyl and cyclohexyl.

5 As used herein, the term “C<sub>2-6</sub>alkenyl” refers to an unsaturated, linear or branched chain alkenyl group containing 2 to 6, particularly 2 to 4 carbon atoms, for example vinyl, propenyl, allyl, butenyl and the like. Particular “C<sub>2-6</sub>alkenyl” group is allyl.

As used herein, the term “C<sub>2-6</sub>alkynyl” refers to an unsaturated, linear or branched chain alkynyl group containing 2 to 6, particularly 2 to 4 carbon atoms, for example ethynyl, 1-  
10 propynyl, propargyl, butynyl and the like. Particular “C<sub>2-6</sub>alkynyl” groups are ethynyl, 1-propynyl and propargyl.

As used herein, the term “C<sub>x</sub>H<sub>2x</sub>” alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms.

As used herein, the term “C<sub>y</sub>H<sub>2y</sub>” or “C<sub>z</sub>H<sub>2z</sub>” alone or in combination signifies a bond or a  
15 saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms.

As used herein, the term “monocyclic heteroaryl” denotes a monovalent aromatic heterocyclic mono- ring system of 5 to 8 ring atoms, comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples of monocyclic  
20 heteroaryl moieties include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, isothiazolyl and the like.

As used herein, the term “N-containing monocyclic heteroaryl” refers to a monocyclic heteroaryl wherein at least one of the heteroatoms is N. Examples for N-containing monocyclic  
25 heteroaryl are pyrrolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, isothiazolyl and the like. Particular “N-containing monocyclic heteroaryl” groups are imidazolyl, pyrazolyl and triazolyl, and more particularly imidazol-1-yl, pyrazol-1-yl and 1,2,4-triazol-1-yl.

As used herein, the term “monocyclic heterocycloalkyl” is a monovalent saturated or partly unsaturated monocyclic ring system of 3 to 7 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples for monocyclic heterocycloalkyl are aziridinyl, oxiranyl, azetidiny, oxetanyl, pyrrolidinyl, 2-oxo-pyrrolidinyl, 5 tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Particular “monocyclic heterocycloalkyl” groups are morpholinyl, 2-oxo-pyrrolidinyl, pyrrolidinyl, tetrahydropyranyl, and more particularly pyrrolidin-1-yl, 2-oxo-10 pyrrolidin-1-yl, tetrahydropyran-4-yl and morpholin-1-yl.

As used herein, the term “diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, activities and reactivities.

15 As used herein, the term “enantiomers” refers to two stereoisomers of a compound which are non-superimposable mirror images of one another.

As used herein, the term “pharmaceutically acceptable salts” refers to salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts. As used herein, the term “prodrug” refers to a form or derivative of a 20 compound which is metabolized in vivo, e.g., by biological fluids or enzymes by a subject after administration, into a pharmacologically active form of the compound in order to produce the desired pharmacological effect. Prodrugs are described e.g. in the Organic Chemistry of Drug Design and Drug Action by Richard B. Silverman, Academic Press, San Diego, 2004, Chapter 8 Prodrugs and Drug Delivery Systems, pp. 497-558.

25 The term “pharmaceutically acceptable acid addition salt” refers to those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic 30 acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic

acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid.

The term “pharmaceutically acceptable base addition salt” refers to those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, and polyamine resins.

As used herein, “hepatitis B virus” or “HBV” refers to a member of the Hepadnaviridae family having a small double-stranded DNA genome of approximately 3,200 base pairs and a tropism for liver cells. “HBV” includes hepatitis B virus that infects any of a variety of mammalian (e.g., human, non-human primate, etc.) and avian (duck, etc.) hosts. “HBV” includes any known HBV genotype, e.g., serotype A, B, C, D, E, F, and G; any HBV serotype or HBV subtype; any HBV isolate; HBV variants, e.g., HBeAg-negative variants, drug-resistant HBV variants (e.g., lamivudine-resistant variants; adefovir-resistant mutants; tenofovir-resistant mutants; entecavir-resistant mutants; etc.); and the like.

As used herein, “HBV DNA” refers to DNA material of HBV.

As used herein, “HBsAg” refers to hepatitis B surface antigen.

As used herein, “HBeAg” refers to hepatitis B e antigen.

As used herein, “HBsAg inhibitor” refers to a compound that inhibits expression of the hepatitis B virus surface antigen. Unless otherwise indicated, an HBsAg inhibitor can include the compound in any pharmaceutically acceptable form, including any isomer (e.g., diastereomer or enantiomer), salt, solvate, polymorph, and the like.

The term "interferon" or "IFN" as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Human interferons are grouped into two classes; Type I, including alpha and beta-interferon, and Type II, which is represented by gamma-interferon only. Recombinant forms of each group have been developed and are commercially available. Subtypes in each group are based on antigenic/structural characteristics.

As used herein, the term "interferon" further includes conjugates, for instance interferon alfa (IFN- $\alpha$ ) conjugates that can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers includes other polyalkylene oxide homopolymers such as polyethylene glycol (PEG), polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer conjugates are described in U.S. Pat. No. 4,766,106, U.S. Pat. No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application Nos. 0510 356, 0 593 868 and 0 809 996 (pegylated interferon alfa-2a) and International Publication No. WO 95/13090.

As used herein the term "pegylated" means covalent conjugates of one or more polyethylene glycol (PEG) molecules and one or more alpha- or beta-type interferon molecules. Preferred conjugates for use in the formulations of the invention have one to four PEG molecules per interferon molecule, and more preferably, the conjugates are between a single PEG molecule and a single interferon molecule. The pegylated interferon may comprise a single positional isomer or a mixture of conjugate positional isomers, e.g, the PEG molecules are covalently attached to different amino acid residues on the individual interferon molecules. For example, U.S. Pat. No. 5,951,974 describes the preparation of mixtures of PEG-interferon alpha conjugate positional isomers in which some of the isomers are conjugates between PEG and a histidine residue of the interferon molecule, other isomers in the mixture are conjugates between PEG and an interferon lysine residue and still other isomers are conjugates between PEG and the amino terminus of the interferon molecule.

As used herein, the "nucleos(t)ide analogue" refers to nucleosides which contain a nucleobase analogue and a sugar and nucleotides which contain a nucleobase analogue, a sugar and one to three phosphate groups. Nucleoside analogue drugs include but are not limited to

deoxyadenosine analogues (Didanosine and Vidarabine), adenosine analogues (BCX4430), deoxycytidine analogues (Cytarabine, Emtricitabine, Lamivudine and Zalcitabine), guanosine and deoxyguanosine analogues (Abacavir, Aciclovir and Entecavir), thymidine and deoxythymidine analogues (Stavudine, Telbivudine and Zidovudine) and deoxyuridine analogues (Idoxuridine and Trifluridine), and pyrimidine analogues (Clevudine). Nucleotide analogue drugs include Adefovir dipivoxil (ADV), Tenofovir disoproxil and Tenofovir disoproxil fumarate (TDF).

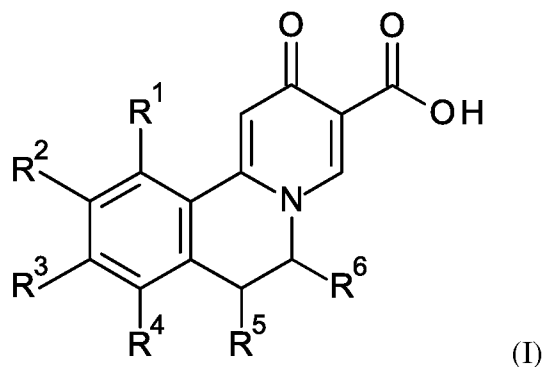
The term "Nucleobase" means any nitrogen-containing heterocyclic moiety capable of forming Watson-Crick-type hydrogen bonds and stacking interactions in pairing with a complementary nucleobase or nucleobase analogue (i.e., derivatives of nucleobases) when that nucleobase is incorporated into a polymeric structure. "Heterocyclic" refers to a molecule with a ring system in which one or more ring atom is a heteroatom, e.g., nitrogen, oxygen, or sulfur (i.e., not carbon).

The term "therapeutically effective amount" refers to an amount of a compound or molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. The therapeutically effective amount will vary depending on the compound, the disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgment of the attending medical or veterinary practitioner, and other factors. The present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor and an interferon, in a pharmaceutically acceptable carrier.

Compounds of the general formula (I) and (II) which contain one or several chiral centers can either be present as racemates, diastereomeric mixtures, or optically active single isomers. The racemates can be separated according to known methods into the enantiomers. Particularly, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid.

The present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon, in a pharmaceutically acceptable carrier.

In one embodiment of the present invention, the “HBsAg inhibitor” is a compound of formula (I):



wherein

- 5  $R^1$  is hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkylamino or  $C_{1-6}$ alkoxy;  
 $R^2$  is hydrogen; halogen;  $C_{1-6}$ alkyl, which is unsubstituted or once, twice or three times substituted by fluoro;  $C_{1-6}$ alkoxy, which is unsubstituted or once, twice or three times substituted by fluoro; cyano;  $C_{3-7}$ cycloalkyl; hydroxy or phenyl- $C_xH_{2x}$ -O-;  
 $R^3$  is hydrogen;  
 10 halogen;  
 $C_{1-6}$ alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; cyano; pyrrolidinyl; amino;  
 15 phenyl- $C_xH_{2x}$ -N( $C_{1-6}$ alkyl)-;  
 $C_{1-6}$ alkoxycarbonylpiperazinyl;  
 or  $R^7$ -O-, wherein  $R^7$  is hydrogen;  $C_{1-6}$ alkyl, which is unsubstituted or substituted with one to three substituents independently selected from fluoro, hydroxy and  $C_{2-6}$ alkenyl;  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl;  $C_{1-6}$ alkoxy $C_{1-6}$ alkoxy $C_{1-6}$ alkyl; amino $C_{1-8}$ alkyl;  $C_{1-6}$ alkylcarbonylamino $C_{1-8}$ alkyl;  $C_{1-6}$ alkylsulfonylamino $C_{1-8}$ alkyl;  $C_{1-6}$ alkylsulfanyl $C_{1-6}$ alkyl;  $C_{1-6}$ alkylsulfonyl $C_{1-6}$ alkyl; cyano $C_{1-6}$ alkyl;  $C_{3-7}$ cycloalkyl $C_{1-6}$ alkyl; cyano $C_{3-7}$ cycloalkyl $C_{1-6}$ alkyl; phenyl $C_{1-6}$ alkyl; pyrrolidinylcarbonyl $C_{1-6}$ alkyl;  $C_{2-6}$ alkynyl; hydroxy $C_{1-6}$ alkyl $C_{2-6}$ alkynyl; amino $C_{1-6}$ alkoxy $C_{1-6}$ alkyl;  $C_{1-6}$ alkylamino $C_{1-6}$ alkoxy $C_{1-6}$ alkyl; di $C_{1-6}$ alkylamino $C_{1-6}$ alkoxy $C_{1-6}$ alkyl; carboxy $C_{1-6}$ alkyl; or  $C_{1-6}$ alkoxycarbonylamino $C_{1-8}$ alkyl;  
 20 heteroaryl $C_{1-6}$ alkyl, wherein heteroaryl is *N*-containing monocyclic heteroaryl; or heterocycloalkyl $C_{1-6}$ alkyl, wherein heterocycloalkyl is monocyclic heterocycloalkyl;  
 25

R<sup>4</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, cyano or C<sub>1-6</sub>alkoxy;

R<sup>5</sup> is hydrogen or C<sub>1-6</sub>alkyl;

R<sup>6</sup> is hydrogen; C<sub>1-6</sub>alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C<sub>3-7</sub>cycloalkyl, which is unsubstituted or once, twice or three times substituted by fluoro or C<sub>1-6</sub>alkyl; or phenyl-C<sub>x</sub>H<sub>2x-</sub>;

x is 1-6;

or pharmaceutically acceptable salts, or enantiomers thereof.

Compounds of formula (I), Compounds 1A to 3A and Compounds 1B to 3B can be obtained according to the synthetic procedures disclosed in WO 2015/113990.

Particularly, the “HBsAg inhibitor” of the present invention relates to

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

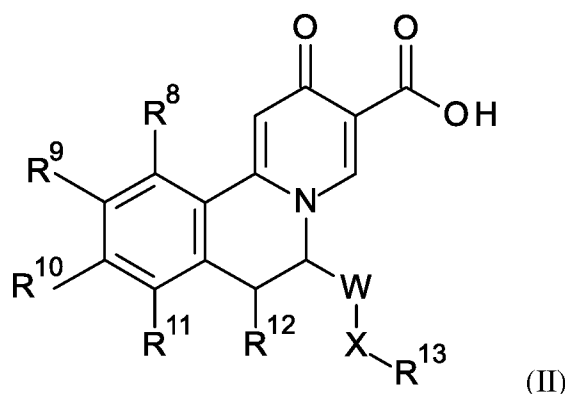
(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or any other compound disclosed in WO 2015/113990;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In another embodiment of the present invention, the “HBsAg inhibitor” is a compound of formula (II):

-13-



wherein

$R^8$ ,  $R^9$ ,  $R^{10}$  and  $R^{11}$  are independently selected from hydrogen, halogen,  $C_{1-6}$ alkyl, di $C_{1-6}$

alkylamino, cyano, *N*-containing monocyclic heterocycloalkyl and  $OR^{14}$ , wherein

5  $R^{14}$  is hydrogen;  $C_{1-6}$ alkyl; or  $C_{1-6}$ alkyl which is substituted once or more times by fluoro,  $C_{3-7}$ cycloalkyl, phenyl, hydroxyl, amino,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkylsulfanyl,  $C_{1-6}$ alkylsulfonyl, di $C_{1-6}$ alkylamino,  $C_{1-6}$ alkoxycarbonylamino, monocyclic heterocycloalkyl, pyrazoyl or imidazolyl;

$R^{12}$  is hydrogen or  $C_{1-6}$ alkyl;

10  $R^{13}$  is hydrogen,  $C_{1-6}$ alkyl, phenyl- $C_xH_{2x-}$ ,  $C_{1-6}$ alkylcarbonyl,  $C_{1-6}$ alkylsulfonyl, benzoyl or monocyclic heterocycloalkyl, wherein  
x is 1-6;

W is a bond,  $C_yH_{2y}C(R^{15})(R^{16})C_zH_{2z}$  or  $C_yH_{2y}CH(R^{15})CH(R^{16})C_zH_{2z}$ , wherein

$R^{15}$  and  $R^{16}$  are independently selected from hydrogen, fluoro, hydroxy and  $C_{1-6}$ alkyl,

15 y is 0-6;

z is 0-6;

X is a bond; O; S;  $S(O)_2$ ; or  $NR^{17}$ , wherein  $R^{17}$  is hydrogen,  $C_{1-6}$ alkyl;

or  $R^{13}$  and  $R^{17}$ , together with the nitrogen to which they are attached, form monocyclic heterocycloalkyl;

20 or pharmaceutically acceptable salts, or enantiomers thereof.

Compounds of formula (II), Compounds 4A to 6A and Compounds 4B to 6B can be obtained according to the synthetic procedures disclosed in WO 2016/071215. Particularly, the “HBsAg inhibitor” of the present invention relates to

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

25 dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

5 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

10 (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Unless otherwise indicated, an HBsAg inhibitor can include any one of the compounds in any pharmaceutically acceptable form, including any isomer (e.g., diastereomer or enantiomer), salt, solvate, polymorph, and the like.

15 In one embodiment of the present invention, suitable nucleos(t)ide analogues of the present invention may be used include nucleoside analogue drugs and nucleotide analogue drugs. Nucleoside analogue drugs include but are not limited to deoxyadenosine analogues (Didanosine and Vidarabine), adenosine analogues (BCX4430), deoxycytidine analogues (Cytarabine, Emtricitabine, Lamivudine and Zalcitabine), guanosine and deoxyguanosine analogues  
20 (Abacavir, Aciclovir and Entecavir), thymidine and deoxythymidine analogues (Stavudine, Telbivudine and Zidovudine), deoxyuridine analogues (Idoxuridine and Trifluridine), and pyrimidine analogues (Clevudine). Nucleotide analogue drugs include but are not limited to Adefovir dipivoxil (ADV), Tenofovir disoproxil and Tenofovir disoproxil fumarate (TDF).

In a particular embodiment of the present invention, the “nucleos(t)ide analogue” is  
25 Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate. More particularly, the “nucleos(t)ide analogue” is Entecavir.

Suitable interferons in accordance with the present invention may be any naturally-occurring or recombinant interferon alfa, beta or gamma known to those skilled in the art.  
30 Natural and recombinant alfa-interferons that may be used include interferon alfa-n1 (e.g.,

Surniferon<sup>®</sup>, Sumitomo), interferon alfa-n3, interferon alfa-2a (Roferon A<sup>®</sup>), interferon alfa-2b (Intron A<sup>®</sup>), interferon alfa-2c (Berofor<sup>®</sup>, Boehringer Ingelheim, Inc.), and consensus interferon (Infergen<sup>®</sup>, InterMune, Inc.). Preferred interferons are interferon alfa-2a and interferon alfa-2b.

5 In one embodiment of the present invention, suitable interferons in accordance with the present invention include, but are not limited to, recombinant interferon alfa-2b such as Intron A<sup>®</sup>; recombinant interferon alfa-2a such as Roferon A<sup>®</sup>; recombinant interferon beta-1b such as Betaferon<sup>®</sup> (Bayer AG); recombinant interferon beta-1a such as Avonex<sup>®</sup> (Biogen Canada Inc.) and Rebif<sup>®</sup> (Merck KGaA); and recombinant interferon gamma-1b such as Imukin<sup>®</sup> (Boehringer Ingelheim). The use of recombinant interferon alfa-2a or alfa-2b is preferred.

10 The terms "interferon alfa-2a", "interferon alfa-2b" and "interferon beta-1a" are further intended to include "pegylated" analogs meaning polyethylene glycol modified conjugates of interferon alfa-2a such as Pegasys<sup>®</sup>, interferon alfa-2b such as PegIntron<sup>®</sup> and Pai Ge Bin, and interferon beta-1a such as Plegridy<sup>®</sup> (Biogen Canada Inc.). The use of pegylated recombinant interferon alfa-2a or alfa 2b is preferred.

15 In one embodiment of the present invention, the "interferon" is a non-conjugated interferon alfa or a pegylated conjugate thereof.

More specifically, the "interferon" is selected from the group consisting of interferon alfa-2a such as Roferon A<sup>®</sup>, interferon alfa-2b such as Intron A<sup>®</sup>, pegylated interferon alfa-2a such as Pegasys<sup>®</sup> and pegylated interferon alfa-2b such as PegIntron<sup>®</sup> and Pai Ge Bin respectively.

20 Obtaining and isolating interferon alfa from natural or recombinant sources is well known (Pestka, Arch. Biochem. Biophys. 221, 1 (1983); European Pat. No. 043980).

Further more specifically, the "interferon" is a non-conjugated interferon alfa-2a (for instance Roferon A<sup>®</sup>) or a pegylated alfa-type interferon (for instance Pegasys<sup>®</sup>):

In yet another embodiment the above pegylated alfa-type interferon is an alfa-2a interferon.

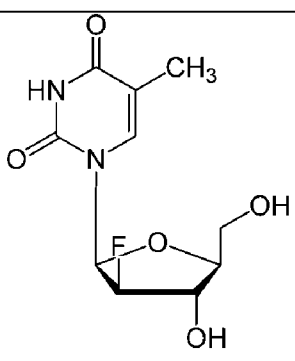
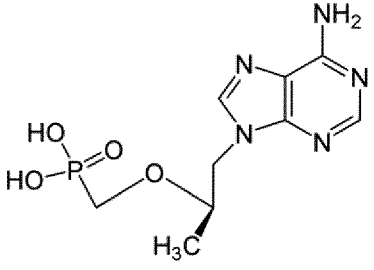
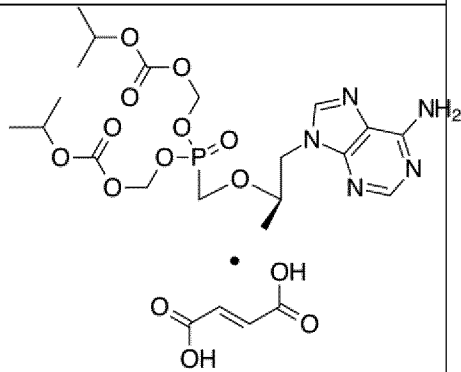
25 In one embodiment of the present invention, the pharmaceutical composition comprises an HBsAg viral expression inhibitor, a nucleos(t)ide analogue and an interferon, wherein the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon are independently selected from Table 1.

Table 1: List of HBsAg inhibitors, interferons and nucleos(t)ide analogues

| Compound Number | Class           | Compound Name                                                                                           | Structure |
|-----------------|-----------------|---------------------------------------------------------------------------------------------------------|-----------|
| 1A              | HBsAg inhibitor | (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid  |           |
| 1B              | HBsAg inhibitor | (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid  |           |
| 2A              | HBsAg inhibitor | (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid   |           |
| 2B              | HBsAg inhibitor | (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid   |           |
| 3A              | HBsAg inhibitor | (+)-6-tert-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid |           |
| 3B              | HBsAg inhibitor | (-)-6-tert-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid |           |

| Compound Number | Class           | Compound Name                                                                                                               | Structure |
|-----------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------|-----------|
| 4A              | HBsAg inhibitor | (+)-10-Methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid |           |
| 4B              | HBsAg inhibitor | (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid |           |
| 5A              | HBsAg inhibitor | (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid |           |
| 5B              | HBsAg inhibitor | (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid |           |
| 6A              | HBsAg inhibitor | (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid  |           |

| Compound Number | Class                  | Compound Name                                                                                                                                          | Structure |
|-----------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 6B              | HBsAg inhibitor        | (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid                             |           |
| 7               | interferon             | interferon alfa-2a (Roferon A <sup>®</sup> )                                                                                                           |           |
| 8               | interferon             | interferon alfa-2b (Intron A <sup>®</sup> )                                                                                                            |           |
| 9               | interferon             | pegylated interferon alfa-2a (Pegasys <sup>®</sup> )                                                                                                   |           |
| 10              | interferon             | pegylated interferon alfa-2b (Pegintron <sup>®</sup> )                                                                                                 |           |
| 11              | interferon             | γ-branched pegylated recombinant human interferon alpha-2b (Pai Ge Bin)                                                                                |           |
| 12              | interferon             | woodchuck interferon alfa-5 (wIFN)                                                                                                                     |           |
| 13              | Nucleos(t)ide analogue | Entecavir (2-amino-9-[(1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> )-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-6,9-dihydro-3 <i>H</i> -purin-6-one) |           |
| 14              | Nucleos(t)ide analogue | Lamivudine (2',3'-dideoxy-3'-thiacytidine)                                                                                                             |           |
| 15              | Nucleos(t)ide analogue | Adefovir dipivoxil ({[2-(6-amino-9 <i>H</i> -purin-9-yl)ethoxy]methyl}phosphonic acid)                                                                 |           |
| 16              | Nucleos(t)ide analogue | Telbivudine (1-(2-deoxy-β- <i>L</i> -erythro-pentofuranosyl)-5-methylpyrimidine-2,4(1 <i>H</i> ,3 <i>H</i> )-dione)                                    |           |

| Compound Number | Class                  | Compound Name                                                                                                                                  | Structure                                                                           |
|-----------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| 17              | Nucleos(t)ide analogue | Clevudine (1-[(2 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i> )-3-fluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione) |  |
| 18              | Nucleos(t)ide analogue | Tenofovir disoproxil (({[(2 <i>R</i> )-1-(6-amino-9 <i>H</i> -purin-9-yl)propan-2-yl]oxy}methyl)phosphonic acid)                               |  |
| 19              | Nucleos(t)ide analogue | Tenofovir disoproxil fumarate                                                                                                                  |  |

More particularly, the present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon which is selected from any one of the following combinations:

Compound 1A, Compound 13 and Compound 7; Compound 1A, Compound 13 and  
 5 Compound 8; Compound 1A, Compound 13 and Compound 9; Compound 1A, Compound 13 and Compound 10; Compound 1A, Compound 13 and Compound 11; Compound 1A, Compound 13 and Compound 12; Compound 1B, Compound 13 and Compound 7; Compound 1B, Compound 13 and Compound 8; Compound 1B, Compound 13 and Compound 9;  
 Compound 1B, Compound 13 and Compound 10; Compound 1B, Compound 13 and Compound  
 10 11; Compound 1B, Compound 13 and Compound 12; Compound 2A, Compound 13 and Compound 7; Compound 2A, Compound 13 and Compound 8; Compound 2A, Compound 13 and Compound 9; Compound 2A, Compound 13 and Compound 10; Compound 2A, Compound 13 and Compound 11; Compound 2A, Compound 13 and Compound 12; Compound 2B,

Compound 13 and Compound 7; Compound 2B, Compound 13 and Compound 8; Compound 2B,  
Compound 13 and Compound 9; Compound 2B, Compound 13 and Compound 10; Compound  
2B, Compound 13 and Compound 11; Compound 2B, Compound 13 and Compound 12;  
Compound 3A, Compound 13 and Compound 7; Compound 3A, Compound 13 and Compound  
8; Compound 3A, Compound 13 and Compound 9; Compound 3A, Compound 13 and  
Compound 10; Compound 3A, Compound 13 and Compound 11; Compound 3A, Compound 13  
and Compound 12; Compound 3B, Compound 13 and Compound 7; Compound 3B, Compound  
13 and Compound 8; Compound 3B, Compound 13 and Compound 9; Compound 3B,  
Compound 13 and Compound 10; Compound 3B, Compound 13 and Compound 11; Compound  
3B, Compound 13 and Compound 12; Compound 4A, Compound 13 and Compound 7;  
Compound 4A, Compound 13 and Compound 8; Compound 4A, Compound 13 and Compound  
9; Compound 4A, Compound 13 and Compound 10; Compound 4A, Compound 13 and  
Compound 11; Compound 4A, Compound 13 and Compound 12; Compound 4B, Compound 13  
and Compound 7; Compound 4B, Compound 13 and Compound 8; Compound 4B, Compound  
13 and Compound 9; Compound 4B, Compound 13 and Compound 10; Compound 4B,  
Compound 13 and Compound 11; Compound 4B, Compound 13 and Compound 12; Compound  
5A, Compound 13 and Compound 7; Compound 5A, Compound 13 and Compound 8;  
Compound 5A, Compound 13 and Compound 9; Compound 5A, Compound 13 and Compound  
10; Compound 5A, Compound 13 and Compound 11; Compound 5A, Compound 13 and  
Compound 12; Compound 5B, Compound 13 and Compound 7; Compound 5B, Compound 13  
and Compound 8; Compound 5B, Compound 13 and Compound 9; Compound 5B, Compound  
13 and Compound 10; Compound 5B, Compound 13 and Compound 11; Compound 5B,  
Compound 13 and Compound 12; Compound 6A, Compound 13 and Compound 7; Compound  
6A, Compound 13 and Compound 8; Compound 6A, Compound 13 and Compound 9;  
Compound 6A, Compound 13 and Compound 10; Compound 6A, Compound 13 and Compound  
11; Compound 6A, Compound 13 and Compound 12; Compound 6B, Compound 13 and  
Compound 7; Compound 6B, Compound 13 and Compound 8; Compound 6B, Compound 13  
and Compound 9; Compound 6B, Compound 13 and Compound 10; Compound 6B, Compound  
13 and Compound 11; Compound 6B, Compound 13 and Compound 12; Compound 1A,  
Compound 14 and Compound 7; Compound 1A, Compound 14 and Compound 8; Compound  
1A, Compound 14 and Compound 9; Compound 1A, Compound 14 and Compound 10;  
Compound 1A, Compound 14 and Compound 11; Compound 1A, Compound 14 and Compound  
12; Compound 1B, Compound 14 and Compound 7; Compound 1B, Compound 14 and



Compound 9; Compound 6B, Compound 14 and Compound 10; Compound 6B, Compound 14 and Compound 11; Compound 6B, Compound 14 and Compound 12; Compound 1A, Compound 15 and Compound 7; Compound 1A, Compound 15 and Compound 8; Compound 1A, Compound 15 and Compound 9; Compound 1A, Compound 15 and Compound 10; 5 Compound 1A, Compound 15 and Compound 11; Compound 1A, Compound 15 and Compound 12; Compound 1B, Compound 15 and Compound 7; Compound 1B, Compound 15 and Compound 8; Compound 1B, Compound 15 and Compound 9; Compound 1B, Compound 15 and Compound 10; Compound 1B, Compound 15 and Compound 11; Compound 1B, Compound 15 and Compound 12; Compound 2A, Compound 15 and Compound 7; Compound 2A, 10 Compound 15 and Compound 8; Compound 2A, Compound 15 and Compound 9; Compound 2A, Compound 15 and Compound 10; Compound 2A, Compound 15 and Compound 11; Compound 2A, Compound 15 and Compound 12; Compound 2B, Compound 15 and Compound 7; Compound 2B, Compound 15 and Compound 8; Compound 2B, Compound 15 and Compound 9; Compound 2B, Compound 15 and Compound 10; Compound 2B, Compound 15 and Compound 11; Compound 2B, Compound 15 and Compound 12; Compound 3A, Compound 15 and Compound 7; Compound 3A, Compound 15 and Compound 8; Compound 3A, Compound 15 and Compound 9; Compound 3A, Compound 15 and Compound 10; Compound 3A, Compound 15 and Compound 11; Compound 3A, Compound 15 and Compound 12; Compound 3B, Compound 15 and Compound 7; Compound 3B, Compound 15 and 20 Compound 8; Compound 3B, Compound 15 and Compound 9; Compound 3B, Compound 15 and Compound 10; Compound 3B, Compound 15 and Compound 11; Compound 3B, Compound 15 and Compound 12; Compound 4A, Compound 15 and Compound 7; Compound 4A, Compound 15 and Compound 8; Compound 4A, Compound 15 and Compound 9; Compound 4A, Compound 15 and Compound 10; Compound 4A, Compound 15 and Compound 11; 25 Compound 4A, Compound 15 and Compound 12; Compound 4B, Compound 15 and Compound 7; Compound 4B, Compound 15 and Compound 8; Compound 4B, Compound 15 and Compound 9; Compound 4B, Compound 15 and Compound 10; Compound 4B, Compound 15 and Compound 11; Compound 4B, Compound 15 and Compound 12; Compound 5A, Compound 15 and Compound 7; Compound 5A, Compound 15 and Compound 8; Compound 5A, Compound 15 and Compound 9; Compound 5A, Compound 15 and Compound 10; Compound 5A, Compound 15 and Compound 11; Compound 5A, Compound 15 and Compound 12; Compound 5B, Compound 15 and Compound 7; Compound 5B, Compound 15 and Compound 8; Compound 5B, Compound 15 and Compound 9; Compound 5B, Compound 15

and Compound 10; Compound 5B, Compound 15 and Compound 11; Compound 5B, Compound 15 and Compound 12; Compound 6A, Compound 15 and Compound 7; Compound 6A, Compound 15 and Compound 8; Compound 6A, Compound 15 and Compound 9; Compound 6A, Compound 15 and Compound 10; Compound 6A, Compound 15 and Compound 11; 5 Compound 6A, Compound 15 and Compound 12; Compound 6B, Compound 15 and Compound 7; Compound 6B, Compound 15 and Compound 8; Compound 6B, Compound 15 and Compound 9; Compound 6B, Compound 15 and Compound 10; Compound 6B, Compound 15 and Compound 11; Compound 6B, Compound 15 and Compound 12; Compound 1A, Compound 16 and Compound 7; Compound 1A, Compound 16 and Compound 8; Compound 10 1A, Compound 16 and Compound 9; Compound 1A, Compound 16 and Compound 10; Compound 1A, Compound 16 and Compound 11; Compound 1A, Compound 16 and Compound 12; Compound 1B, Compound 16 and Compound 7; Compound 1B, Compound 16 and Compound 8; Compound 1B, Compound 16 and Compound 9; Compound 1B, Compound 16 and Compound 10; Compound 1B, Compound 16 and Compound 11; Compound 1B, Compound 15 16 and Compound 12; Compound 2A, Compound 16 and Compound 7; Compound 2A, Compound 16 and Compound 8; Compound 2A, Compound 16 and Compound 9; Compound 2A, Compound 16 and Compound 10; Compound 2A, Compound 16 and Compound 11; Compound 2A, Compound 16 and Compound 12; Compound 2B, Compound 16 and Compound 7; Compound 2B, Compound 16 and Compound 8; Compound 2B, Compound 16 and 20 Compound 9; Compound 2B, Compound 16 and Compound 10; Compound 2B, Compound 16 and Compound 11; Compound 2B, Compound 16 and Compound 12; Compound 3A, Compound 16 and Compound 7; Compound 3A, Compound 16 and Compound 8; Compound 3A, Compound 16 and Compound 9; Compound 3A, Compound 16 and Compound 10; Compound 3A, Compound 16 and Compound 11; Compound 3A, Compound 16 and Compound 25 12; Compound 3B, Compound 16 and Compound 7; Compound 3B, Compound 16 and Compound 8; Compound 3B, Compound 16 and Compound 9; Compound 3B, Compound 16 and Compound 10; Compound 3B, Compound 16 and Compound 11; Compound 3B, Compound 16 and Compound 12; Compound 4A, Compound 16 and Compound 7; Compound 4A, Compound 16 and Compound 8; Compound 4A, Compound 16 and Compound 9; Compound 30 4A, Compound 16 and Compound 10; Compound 4A, Compound 16 and Compound 11; Compound 4A, Compound 16 and Compound 12; Compound 4B, Compound 16 and Compound 7; Compound 4B, Compound 16 and Compound 8; Compound 4B, Compound 16 and Compound 9; Compound 4B, Compound 16 and Compound 10; Compound 4B, Compound 16

and Compound 11; Compound 4B, Compound 16 and Compound 12; Compound 5A,  
Compound 16 and Compound 7; Compound 5A, Compound 16 and Compound 8; Compound  
5A, Compound 16 and Compound 9; Compound 5A, Compound 16 and Compound 10;  
Compound 5A, Compound 16 and Compound 11; Compound 5A, Compound 16 and Compound  
5 12; Compound 5B, Compound 16 and Compound 7; Compound 5B, Compound 16 and  
Compound 8; Compound 5B, Compound 16 and Compound 9; Compound 5B, Compound 16  
and Compound 10; Compound 5B, Compound 16 and Compound 11; Compound 5B, Compound  
16 and Compound 12; Compound 6A, Compound 16 and Compound 7; Compound 6A,  
Compound 16 and Compound 8; Compound 6A, Compound 16 and Compound 9; Compound  
10 6A, Compound 16 and Compound 10; Compound 6A, Compound 16 and Compound 11;  
Compound 6A, Compound 16 and Compound 12; Compound 6B, Compound 16 and Compound  
7; Compound 6B, Compound 16 and Compound 8; Compound 6B, Compound 16 and  
Compound 9; Compound 6B, Compound 16 and Compound 10; Compound 6B, Compound 16  
and Compound 11; Compound 6B, Compound 16 and Compound 12; Compound 1A,  
15 Compound 17 and Compound 7; Compound 1A, Compound 17 and Compound 8; Compound  
1A, Compound 17 and Compound 9; Compound 1A, Compound 17 and Compound 10;  
Compound 1A, Compound 17 and Compound 11; Compound 1A, Compound 17 and Compound  
12; Compound 1B, Compound 17 and Compound 7; Compound 1B, Compound 17 and  
Compound 8; Compound 1B, Compound 17 and Compound 9; Compound 1B, Compound 17  
20 and Compound 10; Compound 1B, Compound 17 and Compound 11; Compound 1B, Compound  
17 and Compound 12; Compound 2A, Compound 17 and Compound 7; Compound 2A,  
Compound 17 and Compound 8; Compound 2A, Compound 17 and Compound 9; Compound  
2A, Compound 17 and Compound 10; Compound 2A, Compound 17 and Compound 11;  
Compound 2A, Compound 17 and Compound 12; Compound 2B, Compound 17 and Compound  
25 7; Compound 2B, Compound 17 and Compound 8; Compound 2B, Compound 17 and  
Compound 9; Compound 2B, Compound 17 and Compound 10; Compound 2B, Compound 17  
and Compound 11; Compound 2B, Compound 17 and Compound 12; Compound 3A,  
Compound 17 and Compound 7; Compound 3A, Compound 17 and Compound 8; Compound  
3A, Compound 17 and Compound 9; Compound 3A, Compound 17 and Compound 10;  
30 Compound 3A, Compound 17 and Compound 11; Compound 3A, Compound 17 and Compound  
12; Compound 3B, Compound 17 and Compound 7; Compound 3B, Compound 17 and  
Compound 8; Compound 3B, Compound 17 and Compound 9; Compound 3B, Compound 17  
and Compound 10; Compound 3B, Compound 17 and Compound 11; Compound 3B, Compound

17 and Compound 12; Compound 4A, Compound 17 and Compound 7; Compound 4A,  
Compound 17 and Compound 8; Compound 4A, Compound 17 and Compound 9; Compound  
4A, Compound 17 and Compound 10; Compound 4A, Compound 17 and Compound 11;  
Compound 4A, Compound 17 and Compound 12; Compound 4B, Compound 17 and Compound  
5 7; Compound 4B, Compound 17 and Compound 8; Compound 4B, Compound 17 and  
Compound 9; Compound 4B, Compound 17 and Compound 10; Compound 4B, Compound 17  
and Compound 11; Compound 4B, Compound 17 and Compound 12; Compound 5A,  
Compound 17 and Compound 7; Compound 5A, Compound 17 and Compound 8; Compound  
5A, Compound 17 and Compound 9; Compound 5A, Compound 17 and Compound 10;  
10 Compound 5A, Compound 17 and Compound 11; Compound 5A, Compound 17 and Compound  
12; Compound 5B, Compound 17 and Compound 7; Compound 5B, Compound 17 and  
Compound 8; Compound 5B, Compound 17 and Compound 9; Compound 5B, Compound 17  
and Compound 10; Compound 5B, Compound 17 and Compound 11; Compound 5B, Compound  
17 and Compound 12; Compound 6A, Compound 17 and Compound 7; Compound 6A,  
15 Compound 17 and Compound 8; Compound 6A, Compound 17 and Compound 9; Compound  
6A, Compound 17 and Compound 10; Compound 6A, Compound 17 and Compound 11;  
Compound 6A, Compound 17 and Compound 12; Compound 6B, Compound 17 and Compound  
7; Compound 6B, Compound 17 and Compound 8; Compound 6B, Compound 17 and  
Compound 9; Compound 6B, Compound 17 and Compound 10; Compound 6B, Compound 17  
20 and Compound 11; Compound 6B, Compound 17 and Compound 12; Compound 1A,  
Compound 18 and Compound 7; Compound 1A, Compound 18 and Compound 8; Compound  
1A, Compound 18 and Compound 9; Compound 1A, Compound 18 and Compound 10;  
Compound 1A, Compound 18 and Compound 11; Compound 1A, Compound 18 and Compound  
12; Compound 1B, Compound 18 and Compound 7; Compound 1B, Compound 18 and  
25 Compound 8; Compound 1B, Compound 18 and Compound 9; Compound 1B, Compound 18  
and Compound 10; Compound 1B, Compound 18 and Compound 11; Compound 1B, Compound  
18 and Compound 12; Compound 2A, Compound 18 and Compound 7; Compound 2A,  
Compound 18 and Compound 8; Compound 2A, Compound 18 and Compound 9; Compound  
2A, Compound 18 and Compound 10; Compound 2A, Compound 18 and Compound 11;  
30 Compound 2A, Compound 18 and Compound 12; Compound 2B, Compound 18 and Compound  
7; Compound 2B, Compound 18 and Compound 8; Compound 2B, Compound 18 and  
Compound 9; Compound 2B, Compound 18 and Compound 10; Compound 2B, Compound 18  
and Compound 11; Compound 2B, Compound 18 and Compound 12; Compound 3A,

Compound 18 and Compound 7; Compound 3A, Compound 18 and Compound 8; Compound 3A, Compound 18 and Compound 9; Compound 3A, Compound 18 and Compound 10; Compound 3A, Compound 18 and Compound 11; Compound 3A, Compound 18 and Compound 12; Compound 3B, Compound 18 and Compound 7; Compound 3B, Compound 18 and  
5 Compound 8; Compound 3B, Compound 18 and Compound 9; Compound 3B, Compound 18 and Compound 10; Compound 3B, Compound 18 and Compound 11; Compound 3B, Compound 18 and Compound 12; Compound 4A, Compound 18 and Compound 7; Compound 4A, Compound 18 and Compound 8; Compound 4A, Compound 18 and Compound 9; Compound 4A, Compound 18 and Compound 10; Compound 4A, Compound 18 and Compound 11;  
10 Compound 4A, Compound 18 and Compound 12; Compound 4B, Compound 18 and Compound 7; Compound 4B, Compound 18 and Compound 8; Compound 4B, Compound 18 and Compound 9; Compound 4B, Compound 18 and Compound 10; Compound 4B, Compound 18 and Compound 11; Compound 4B, Compound 18 and Compound 12; Compound 5A, Compound 18 and Compound 7; Compound 5A, Compound 18 and Compound 8; Compound  
15 5A, Compound 18 and Compound 9; Compound 5A, Compound 18 and Compound 10; Compound 5A, Compound 18 and Compound 11; Compound 5A, Compound 18 and Compound 12; Compound 5B, Compound 18 and Compound 7; Compound 5B, Compound 18 and Compound 8; Compound 5B, Compound 18 and Compound 9; Compound 5B, Compound 18 and Compound 10; Compound 5B, Compound 18 and Compound 11; Compound 5B, Compound  
20 18 and Compound 12; Compound 6A, Compound 18 and Compound 7; Compound 6A, Compound 18 and Compound 8; Compound 6A, Compound 18 and Compound 9; Compound 6A, Compound 18 and Compound 10; Compound 6A, Compound 18 and Compound 11; Compound 6A, Compound 18 and Compound 12; Compound 6B, Compound 18 and Compound 7; Compound 6B, Compound 18 and Compound 8; Compound 6B, Compound 18 and  
25 Compound 9; Compound 6B, Compound 18 and Compound 10; Compound 6B, Compound 18 and Compound 11; Compound 6B, Compound 18 and Compound 12; Compound 1A, Compound 19 and Compound 7; Compound 1A, Compound 19 and Compound 8; Compound 1A, Compound 19 and Compound 9; Compound 1A, Compound 19 and Compound 10; Compound 1A, Compound 19 and Compound 11; Compound 1A, Compound 19 and Compound  
30 12; Compound 1B, Compound 19 and Compound 7; Compound 1B, Compound 19 and Compound 8; Compound 1B, Compound 19 and Compound 9; Compound 1B, Compound 19 and Compound 10; Compound 1B, Compound 19 and Compound 11; Compound 1B, Compound 19 and Compound 12; Compound 2A, Compound 19 and Compound 7; Compound 2A,

Compound 19 and Compound 8; Compound 2A, Compound 19 and Compound 9; Compound 2A, Compound 19 and Compound 10; Compound 2A, Compound 19 and Compound 11; Compound 2A, Compound 19 and Compound 12; Compound 2B, Compound 19 and Compound 7; Compound 2B, Compound 19 and Compound 8; Compound 2B, Compound 19 and  
5 Compound 9; Compound 2B, Compound 19 and Compound 10; Compound 2B, Compound 19 and Compound 11; Compound 2B, Compound 19 and Compound 12; Compound 3A, Compound 19 and Compound 7; Compound 3A, Compound 19 and Compound 8; Compound 3A, Compound 19 and Compound 9; Compound 3A, Compound 19 and Compound 10; Compound 3A, Compound 19 and Compound 11; Compound 3A, Compound 19 and Compound  
10 12; Compound 3B, Compound 19 and Compound 7; Compound 3B, Compound 19 and Compound 8; Compound 3B, Compound 19 and Compound 9; Compound 3B, Compound 19 and Compound 10; Compound 3B, Compound 19 and Compound 11; Compound 3B, Compound 19 and Compound 12; Compound 4A, Compound 19 and Compound 7; Compound 4A, Compound 19 and Compound 8; Compound 4A, Compound 19 and Compound 9; Compound  
15 4A, Compound 19 and Compound 10; Compound 4A, Compound 19 and Compound 11; Compound 4A, Compound 19 and Compound 12; Compound 4B, Compound 19 and Compound 7; Compound 4B, Compound 19 and Compound 8; Compound 4B, Compound 19 and Compound 9; Compound 4B, Compound 19 and Compound 10; Compound 4B, Compound 19 and Compound 11; Compound 4B, Compound 19 and Compound 12; Compound 5A,  
20 Compound 19 and Compound 7; Compound 5A, Compound 19 and Compound 8; Compound 5A, Compound 19 and Compound 9; Compound 5A, Compound 19 and Compound 10; Compound 5A, Compound 19 and Compound 11; Compound 5A, Compound 19 and Compound 12; Compound 5B, Compound 19 and Compound 7; Compound 5B, Compound 19 and Compound 8; Compound 5B, Compound 19 and Compound 9; Compound 5B, Compound 19  
25 and Compound 10; Compound 5B, Compound 19 and Compound 11; Compound 5B, Compound 19 and Compound 12; Compound 6A, Compound 19 and Compound 7; Compound 6A, Compound 19 and Compound 8; Compound 6A, Compound 19 and Compound 9; Compound 6A, Compound 19 and Compound 10; Compound 6A, Compound 19 and Compound 11; Compound 6A, Compound 19 and Compound 12; Compound 6B, Compound 19 and Compound  
30 7; Compound 6B, Compound 19 and Compound 8; Compound 6B, Compound 19 and Compound 9; Compound 6B, Compound 19 and Compound 10; Compound 6B, Compound 19 and Compound 11; and Compound 6B, Compound 19 and Compound 12; in a pharmaceutically acceptable carrier.

Anyone of Compounds 1A to 6A, 1B to 6B and 7 to 11 of the aforementioned combinations can be replaced by its corresponding pharmaceutically acceptable salt, enantiomer or diastereomer, which is another aspect of this invention.

More particularly, the present invention relates to a pharmaceutical composition  
5 comprising an HBsAg inhibitor and an interferon which is selected from any one of the following combinations:

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
10 dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

15 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
20 dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

25 (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-  
30 dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-  
3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

5 (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

10 (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

15 (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

20 (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

25 (+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

30 (+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

5 (-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

10 (-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

15 (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

20 (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

25 (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

30 (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron®;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

5 (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A®;

10 (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A®;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys®;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron®;

15 (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

20 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A®;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A®;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys®;

25 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron®;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

30 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A®;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

5 (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

10 (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

15 (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

20 (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin; and

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

in a pharmaceutically acceptable carrier.

25 In another particular embodiment of the present invention, the nucleos(t)ide analogue used in the combination is Lamivudine, Adefovir dipivoxil, Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate.

In one embodiment of the present invention, the pharmaceutical composition consists of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon, in a pharmaceutically acceptable carrier. More particularly, the composition consists of:

30 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>; or

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

in a pharmaceutically acceptable carrier.

In another embodiment of the present invention, other interferons, nucleos(t)ide analogues or HBsAg inhibitors can also be used in the pharmaceutical composition including small molecules or large molecules. Examples of other interferons include, but not limited to,

5 Surniferon, Sumitomo, Berofor, Infergen, Multiferon, Rebif, Avonex, Cinnovex, Betaseron / Betaferon, Imukin, Plegridy, Actimmune, Reiferon Retard and Pegetron.

Typical dosages of an HBsAg inhibitor, a nucleos(t)ide analogue and/or an interferon can be in the ranges recommended by the manufacturer, and where indicated by *in vitro* responses in an animal model, can be reduced by up to about one order of magnitude concentration or amount.

10 Thus, the actual dosage will depend upon the judgment of the physician, the condition of the patient, and the effectiveness of the therapeutic method based on the *in vitro* responsiveness of the appropriate animal models.

Another embodiment of the present invention relates to a method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that an

15 HBsAg inhibitor, a nucleos(t)ide analogue and an interferon are used in the medicament.

A further embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon are co-administered in the same formulation or different formulation.

20 For purposes of the present invention, "co-administer" refers to any administration of the HBsAg inhibitor, the nucleos(t)ide analogue and interferon as the three active agents, either separately or together, where the three active agents are administered as part of an appropriate dose regimen designed to obtain the benefit of the combination therapy. Thus, the three active agents can be administered either as part of the same pharmaceutical composition or in separate  
25 pharmaceutical compositions. Also, the three active agents can be administered either at the same time, or sequentially.

The pharmaceutical composition of the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon can be administered with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozengens, troches, hard candies, powders, sprays, creams, salves,  
30 suppositories, jellies, gels, pastes, lotions, ointments, elixirs, syrups, and the like. Administration

of such dosage forms can be carried out in single or multiple doses. Carriers include solid diluents of fillers, sterile aqueous media and various non-toxic organic solvents. Administration of such dosage forms can be carried out through, but not limited to, oral administration, parenteral administration, veterinary administration.

5           A further embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon are intended for administration to a subject by the same route or different routes.

10           A further embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon thereof are intended for administration to a subject by parenteral or oral administration.

15           A further embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the administration of the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon thereof to a subject is simultaneous or sequential. In any of the methods of the present invention, the administration of agents simultaneously can be performed by separately or sequentially administering agents at the same time, or together as a fixed combination. Also, in any of the methods of the present invention, the administration of agents separately or sequentially can be  
20 in any order.

          Another embodiment of the present invention relates to the method for manufacturing a medicament of composition for treatment or prophylaxis of hepatitis B virus infection, characterized in that HBsAg inhibitor thereof is a compound of formula (I), or formula (II), or pharmaceutically acceptable salt, enantiomer or diastereomer thereof. Particularly, the HBsAg  
25 inhibitor thereof is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

30           (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

5 (-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

10 (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

15 (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

20 Another embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the nucleos(t)ide analogue is Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate. Particularly the nucleos(t)ide analogue is Entecavir.

25 Another embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the interferon thereof is a non-conjugated interferon alfa, a pegylated alfa-type interferon or a y-branched pegylated recombinant human interferon alpha-2b; particularly the interferon is Roferon A<sup>®</sup>, Intron A<sup>®</sup>, Pegasys<sup>®</sup>, PegIntron<sup>®</sup>, Pai Ge Bin or wIFN; more particularly the  
30 interferon is Pegasys<sup>®</sup> or wIFN.

Another embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon used in the medicament are

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

5 dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys®; or

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

in a pharmaceutically acceptable carrier.

Another embodiment of the present invention relates to a kit comprising a container  
10 comprising an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon, said kit can further comprise a sterile diluent.

A further embodiment of the present invention relates to the said kit, wherein the kit can further comprise a package insert comprising printed instructions directing the use of a combined treatment of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon as a method for  
15 treatment or prophylaxis of hepatitis B virus infection.

Another embodiment of the present invention relates to the said kit, wherein the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

20 (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

25 (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

30 (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

5 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

10 (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;  
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of present invention relates to the said kit, characterized in that the nucleos(t)ide analogue is Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate. Particularly the nucleos(t)ide analogue is  
15 Entecavir.

Another embodiment of the present invention relates to the said kit, characterized in that the interferon thereof is a non-conjugated interferon alfa, a pegylated alfa-type interferon or a y-branched pegylated recombinant human interferon alpha-2b; particularly the interferon is Roferon A<sup>®</sup>, Intron A<sup>®</sup>, Pegasys<sup>®</sup>, PegIntron<sup>®</sup>, Pai Ge Bin or wIFN; more particularly the  
20 interferon is Pegasys<sup>®</sup> or wIFN.

Another embodiment of the present invention relates to the said kit, characterized in that the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon used in the container are

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>; or

25 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

or pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention relates to a method for the treatment or prophylaxis of hepatitis B virus infection, comprising administration to a subject with an  
30 effective amount of an HBsAg inhibitor, or pharmaceutically acceptable salt, enantiomer or

diastereomer thereof; an effective amount of a nucleos(t)ide analogue and an effective amount of an interferon; wherein the HBsAg inhibitor thereof is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

5 (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

10 (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

15 (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

20 (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

25 (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the present invention relates to a method for the treatment or prophylaxis of hepatitis B virus infection, comprising administration to a subject with an  
30 effective amount of an HBsAg inhibitor, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof; an effective amount of a nucleos(t)ide analogue and an effective amount of an interferon, wherein the nucleos(t)ide analogue is Lamivudine, Adefovir dipivoxil, Entecavir,

Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate. Particularly the nucleos(t)ide analogue is Entecavir.

Another embodiment of the present invention relates to a method for the treatment or prophylaxis of hepatitis B virus infection, comprising administration to a subject with an effective amount of an HBsAg inhibitor, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof; an effective amount of a nucleos(t)ide analogue and an effective amount of an interferon, wherein the interferon thereof is a non-conjugated interferon alfa, a pegylated alfa-type interferon or a y-branched pegylated recombinant human interferon alpha-2b; particularly the interferon is Roferon A<sup>®</sup>, Intron A<sup>®</sup>, Pegasys<sup>®</sup>, PegIntron<sup>®</sup>, Pai Ge Bin or wIFN; more particularly the interferon is Pegasys<sup>®</sup> or wIFN.

A further embodiment of the present invention relates to a method for the treatment or prophylaxis of hepatitis B virus infection, wherein the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon used in the subject are

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>; or  
(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;  
in a pharmaceutically acceptable carrier.

Another embodiment of the present invention relates to use of the pharmaceutical composition herein mentioned above as an antiviral medicament, in particular as the medicament for treatment or prophylaxis of hepatitis B virus infection.

Another embodiment of the present invention relates to the use of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon for the manufacture of the pharmaceutical composition herein mentioned above as an antiviral medicament, in particular the medicament for treatment or prophylaxis of hepatitis B virus infection.

## **EXAMPLES**

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

## **ABBREVIATIONS**

-40-

|    |           |                                                          |
|----|-----------|----------------------------------------------------------|
|    | CI        | Combination index                                        |
|    | CTG       | CellTiter-Glo®                                           |
|    | FBS       | Fetal Bovine Serum                                       |
|    | FIC       | Fractional inhibition concentration                      |
| 5  | GE        | Genome equivalent                                        |
|    | HBsAg     | Hepatitis B surface antigen                              |
|    | IU        | International units                                      |
|    | nM        | Nanomolar                                                |
|    | PBS       | Phosphate buffered saline                                |
| 10 | PEG       | Polyethyleneglycol                                       |
|    | Pen/Strep | Penicillin/Streptomycin                                  |
|    | qPCR      | Real-time quantitative polymerase chain reaction         |
|    | SD        | Standard deviation                                       |
|    | Sec       | Second                                                   |
| 15 | UDG       | Uracil DNA glycosylase                                   |
|    | PXB       | Phoenix Bio                                              |
|    | h-Alb     | Human albumin                                            |
|    | WHV       | Woodchuck hepatitis virus                                |
|    | anti-WHs  | Antibody against the woodchuck hepatitis surface antigen |
| 20 | WHV DNA   | Woodchuck hepatitis virus DNA                            |
|    | WHsAg     | Woodchuck hepatitis surface antigen                      |
|    | anti-WHc  | Antibody against the woodchuck hepatitis core antigen    |
|    | GGT       | Gamma-glutamyltransferase                                |
|    | SDH       | Sorbitol dehydrogenase                                   |
| 25 | p.o.      | per os                                                   |
|    | s.c.      | subcutaneous                                             |
|    | QD        | once daily                                               |
|    | BIW       | twice weekly                                             |

30

**Example 1**

**Combination of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon, in HBV infected PXB mice**

**Compound treatment of HBV infected PXB mice**

Four days prior to the first administration (Day -4), all the candidate HBV infected PXB mice (PhoenixBio Co., Ltd., 3-4-1, Kagamiyama, Higashi-Hiroshima, 739-0046 Japan) were weighed and those with a healthy appearance and which met all of the following criteria were assigned to the study.

- 5 Genotype: cDNA-uPAwild/+ /SCID (cDNA-uPAwild/+; B6; 129SvEv-Plau, SCID: C.B-17/Icr-scid /scid Jcl)  
 Age: 19-weeks or more on Day 0 (Actual ages on Day 0: from 21 to 25-weeks)  
 Gender: Male  
 Weight: 16.4 g or more on Day -4 (Actual weights on Day -4: from 16.5 to 23.7 g)
- 10 Blood h-Alb level: Not specified (Actual levels on Day -10: from 8.5 to 15.5 mg/mL)  
 HBV genotype: C (Code No.: PBB004, Lot: 140309, PhoenixBio Co., Ltd.)  
 Serum HBV DNA level:  $1.0 \times 10^6$  copies/mL or more on Day -10 (plateau)  
 (Actual levels on Day -10: from  $2.5 \times 10^6$  to  $4.8 \times 10^8$  copies/mL)  
 Donor of hepatocytes: BD195 (BD Biosciences, Woburn, MA, USA)
- 15 To minimize variance between the groups, the group composition was randomized based on the arithmetic mean values for body weight and geometric mean values for blood h-Alb concentration and serum HBV DNA concentration. Mice were assigned to groups and treated with single compounds or combinations of compounds for 35 days as summarized in Table 2.

Table 2. Treatment groups and dose levels

| Group | Number of mice | Compound    | Dose          |       | Frequency                                                    |
|-------|----------------|-------------|---------------|-------|--------------------------------------------------------------|
|       |                |             | Level (mg/kg) | Route |                                                              |
| 1     | 5              | Vehicle     | 0             | p.o.  | QD, for 35 days (days 0 to 34)                               |
| 2     | 5              | Compound 1A | 10            | p.o.  | QD, for 35 days (days 0 to 34)                               |
| 3     | 5              | Compound 13 | 0.03          | p.o.  | QD, for 35 days (days 0 to 34)                               |
| 4     | 5              | Compound 9  | 0.025         | s.c.  | BIW, for 35 days, (days 0, 3, 7, 10, 14, 17, 21, 24, 28, 31) |
| 5     | 5              | Compound 1A | 10            | p.o.  | QD, for 35 days (days 0 to 34)                               |
|       |                | Compound 13 | 0.03          | p.o.  | QD, for 35 days (days 0 to 34)                               |
| 6     | 5              | Compound 1A | 10            | p.o.  | QD, for 35 days (days 0 to 34)                               |
|       |                | Compound 13 | 0.03          | p.o.  | QD, for 35 days (days 0 to 34)                               |

|  |  |            |       |      |                                                                    |
|--|--|------------|-------|------|--------------------------------------------------------------------|
|  |  | Compound 9 | 0.025 | s.c. | BIW, for 35 days,<br>(days 0, 3, 7, 10, 14,<br>17, 21, 24, 28, 31) |
|--|--|------------|-------|------|--------------------------------------------------------------------|

### HBV DNA quantification in mouse serum

HBV DNA was extracted from 5  $\mu$ L of serum using the SMITEST EX-R&D Nucleic Acid Extraction Kit (MEDICAL & BIOLOGICAL LABORATORIES CO., LTD., Nagoya, Japan). The DNA was dissolved in 20  $\mu$ L nuclease-free water (Life Technologies Corporation, Carlsbad, CA, USA).

Serum from an HBV-infected PXB-mouse was used as the HBV DNA standard. Synthetic HBV DNA was used to determine the concentration of the HBV DNA standard which had been divided into aliquots and stored at  $-80^{\circ}\text{C}$  until the quantification of the serum HBV DNA level. The HBV DNA was extracted from the HBV DNA standard and used for real-time PCR after appropriate dilution. For this study, the range of the standard used was between  $4.0 \times 10^4$  and  $2.0 \times 10^9$  copies/mL.

The real-time detection PCR to measure the serum HBV DNA concentration was performed using the TaqMan Fast Advanced Master Mix (Life Technologies Corporation, Carlsbad, CA, USA) and ABI Prism 7500 sequence detector system (Life Technologies Corporation). The PCR reaction mixture was added into 5  $\mu$ L of the extracted DNA. The initial activation of uracil-N-glycosylase at  $50^{\circ}\text{C}$  for 2 minutes was followed by the polymerase activation at  $95^{\circ}\text{C}$  for 20 seconds. Subsequent PCR amplification consisted of 53 cycles of denaturation at  $95^{\circ}\text{C}$  for 3 seconds and annealing and extension at  $60^{\circ}\text{C}$  for 32 seconds per cycle in an ABI 7500 sequence detector. The average serum HBV DNA level was calculated from the values of the two separate wells.

The primers and probe consisted of the following sequence given in Table 3 respectively:

Table 3. Sequences of the primers and probe used for HBV DNA quantification

| Identification | Target Location | Sequence Information |    |             |     |
|----------------|-----------------|----------------------|----|-------------|-----|
|                |                 | Dye                  | 5' | Nucleotides | 3'  |
|                |                 |                      |    |             | Dye |

|                              |         |     |                            |       |
|------------------------------|---------|-----|----------------------------|-------|
| Forward primer<br>(SEQ ID 1) | 166-186 | n/a | CACATCAGGATTCCTAGGACC      | n/a   |
| Reverse primer<br>(SEQ ID 2) | 344-325 | n/a | AGGTTGGTGAGTGATTGGAG       | n/a   |
| TaqMan probe<br>(SEQ ID 3)   | 242-267 | FAM | CAGAGTCTAGACTCGTGGTGGACTTC | TAMRA |

The lowest quantification limit of this assay was  $4.0 \times 10^4$  copies/mL serum.

### Hepatitis B surface antigen (HBsAg) quantification in mouse serum

Serum HBsAg concentration was determined by SRL, Inc. (Tokyo, Japan) based on ChemiLuminescence ImmunoAssay (CLIA) developed by Abbott (ARCHITECT® SYSTEM).

- 5 The dilution factor was 60, and the measurement range of this assay was between 0.05 and 250 IU/mL. For the 60-fold diluted samples, the measurement range was adjusted to be between 3.0 and 15000 IU/mL.

### Results

- 10 The antiviral effects of Compound 1A, Compound 9, and Compound 13 alone or in combination against HBV determined by the serum HBV DNA concentration were summarized in Table 4.

Table 4: Antiviral effect of single drugs and drug combinations on HBV DNA

| Group | Test compounds                             | Dose level (mg/kg)    | Maximum antiviral effects |                                |
|-------|--------------------------------------------|-----------------------|---------------------------|--------------------------------|
|       |                                            |                       | Time Point (Day)          | Log Ratio to the Initial Value |
| 1     | Vehicle                                    | 0                     | 28                        | -0.03                          |
| 2     | Compound 1A                                | 10                    | 28, 35                    | -0.69                          |
| 3     | Compound 13                                | 0.03                  | 28                        | -2.36                          |
| 4     | Compound 9                                 | 0.025                 | 35                        | -1.80                          |
| 5     | Compound 1A and Compound 13 and Compound 9 | 10 and 0.03 and 0.025 | 35                        | -3.37                          |

- 15 The HBV DNA concentration decrease with the therapy of combination of Compound 1A plus Compound 13 plus Compound 9 was most evident and was measured to be -3.37 log from the initial level.

The antiviral effects of Compound 1A, Compound 9 and Compound 13 alone or in combination against HBV determined by the serum HBsAg concentration were summarized in Table 5.

Table 5. Antiviral effect of single drugs and drug combinations on HBsAg

| Group | Test compounds                             | Dose level (mg/kg)    | Maximum antiviral effects |                                |
|-------|--------------------------------------------|-----------------------|---------------------------|--------------------------------|
|       |                                            |                       | Time Point (Day)          | Log Ratio to the Initial Value |
| 1     | Vehicle                                    | 0                     | 24, 35                    | -0.05                          |
| 2     | Compound 1A                                | 10                    | 35                        | -0.75                          |
| 3     | Compound 13                                | 0.03                  | 42                        | -0.35                          |
| 4     | Compound 9                                 | 0.025                 | 35                        | -0.45                          |
| 5     | Compound 1A and Compound 13 and Compound 9 | 10 and 0.03 and 0.025 | 35                        | -1.16                          |

- 5 The HBsAg concentration decrease with the therapy of combination of Compound 1A plus Compound 13 plus Compound 9 was most evident and was measured to be -1.16 Log from the initial level.

## Example 2

### 10 Combination of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon, in woodchucks

#### Infection and compound treatment of woodchucks

- Woodchucks were born in captivity and were infected at 3 days of age with WHV strain WHV7-11. Chronically infected animals were all anti-WHs negative, with detectable serum WHV DNA, WHsAg and anti-WHc at approximately 1 year post-infection. Absence of liver tumors in woodchucks with low GGT was confirmed by ultrasonography. Chronic WHV carrier woodchucks were assigned and stratified by gender, body weight, and by pretreatment serum markers (WHsAg and WHV DNA concentrations, serum GGT and SDH activities) into the treatment groups as summarized in Figure 1.

Compound treatment of the woodchucks was performed for 14 weeks. Compound 13 (0.1 mg/kg) and Compound 1A (10 mg/kg), alone or in combination, were orally administered twice a day. Compound 12 (100 µg/woodchuck) was administered in addition to Compound 13 and/or Compound 1A subcutaneously as follows: three times per week (TIW) for week 0 to 2, no treatment for week 2 to 4, and two times per week (BID) for week 6 to 14. The study design is summarized in Figure 1.

Blood samples were drawn from woodchucks once per week and used to determine WHsAg levels.

### Measurement of WHsAg

Serum WHsAg was measured by WHV-specific enzyme immunoassays as described in (Cote PJ, Roneker C, Cass K, Schodel F, Peterson D, et al. (1993) New enzyme immunoassays for the serologic detection of woodchuck hepatitis virus infection. *Viral Immunol* 6: 161–169. PMID: 8216715).

### Results

As shown in Figure 2, Compound 13 alone and Compound 1A alone showed mean log<sub>10</sub> reductions of -1.4 and -1.7 for WHsAg, respectively, on week 14 compared to baseline levels. Two-drug combination of Compound 1A with Compound 13 resulted in an increased WHsAg log<sub>10</sub> reduction of -3.4. The highest inhibition of WHsAg was observed with the triple therapy of combination of Compound 1A and Compound 13 and Compound 12 (-4.7 log<sub>10</sub> reduction).

Effect of combination of Compound 1A and Compound 13 and Compound 12 on WHsAg was analyzed according to the Bliss independence method (Zhao W. et al., A New Bliss Independence Model to Analyze Drug Combination Data. *J Biomol Screen*. 2014 Jun;19(5):817-21; J. Fouquier & M. Guedj, Analysis of drug combinations: current methodological landscape. *Pharmacol Res Perspect*. 2015 Jun;3(3):e00149). Inhibition values were calculated from the measured WHsAg raw data values using equation:

$$\text{Inhibition} = 1 - (\text{WHsAg at day } x / \text{WHsAg at day } 0).$$

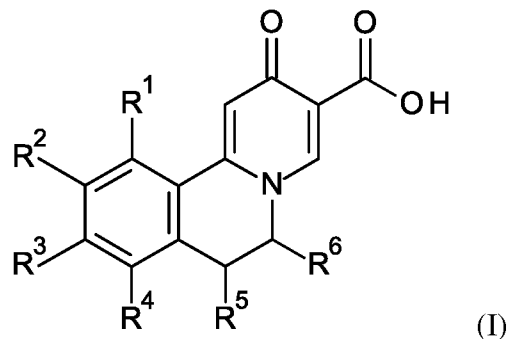
The predicted effect assuming additivity of the triple combination was then calculated based on the inhibition values of the single drugs using equation:  $Y_{ab,P} = Y_a + Y_b - Y_a Y_b$ , meaning drug A at dose a inhibits  $Y_a$  of WHsAg and drug B at dose b inhibits  $Y_b$  of WHsAg. In this analysis, drug A was defined as Compound 1A and drug B was defined as combination of

Compound 12 and Compound 13. Values were transformed using equation: %WHsAg =  $(1 - Y_{ab,p}) \times 100$  and plotted against the time. As shown in Figure 4, most of the 95% confidence intervals of the triple combination effects are below the predicted additive effects and do not overlap with these, suggesting that triple combination of Compound 1A and Compound 13 and  
5 Compound 12 show a synergistic effect on WHsAg inhibition.

## CLAIMS

1. A pharmaceutical composition comprising an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon, in a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim 1, wherein the HBsAg inhibitor is a compound of formula (I):



wherein

- R<sup>1</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylamino or C<sub>1-6</sub>alkoxy;

- R<sup>2</sup> is hydrogen; halogen; C<sub>1-6</sub>alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C<sub>1-6</sub>alkoxy, which is unsubstituted or once, twice or three times substituted by fluoro; cyano; C<sub>3-7</sub>cycloalkyl; hydroxy or phenyl-C<sub>x</sub>H<sub>2x</sub>-O-;

- $R^3$  is hydrogen;

halogen;

C<sub>1-6</sub>alkyl, which is unsubstituted or once, twice or three times substituted by fluoro;

cyano;

pyrrolidinyl;

amino;

phenyl-C<sub>x</sub>H<sub>2x</sub>-N(C<sub>1-6</sub>alkyl)-;

C<sub>1-6</sub>alkoxycarbonylpiperazinyl;

or R<sup>7</sup>-O-, wherein R<sup>7</sup> is hydrogen; C<sub>1-6</sub>alkyl, which is unsubstituted or substituted with one to three substituents independently selected from fluoro, hydroxy and C<sub>2-6</sub>alkenyl; C<sub>1</sub>-

$$_6\text{alkoxyC}_{1-6}\text{alkyl}; \text{C}_{1-6}\text{alkoxyC}_{1-6}\text{alkoxyC}_{1-6}\text{alkyl}; \text{aminoC}_{1-8}\text{alkyl}; \text{C}_{1-}$$
$$\text{alkylcarbonylaminoC}_{1-8}\text{alkyl}; \text{C}_{1-6}\text{alkylsulfonylaminoC}_{1-8}\text{alkyl}; \text{C}_{1-6}\text{alkylsulfanylC}_{1-6}\text{alkyl};$$

C<sub>1-6</sub>alkylsulfonylC<sub>1-6</sub>alkyl; cyanoC<sub>1-6</sub>alkyl; C<sub>3-7</sub>cycloalkylC<sub>1-6</sub>alkyl; cyanoC<sub>3-7</sub>cycloalkylC<sub>1-</sub>

6alkyl; phenylC<sub>1-6</sub>alkyl; pyrrolidinylcarbonylC<sub>1-6</sub>alkyl; C<sub>2-6</sub>alkynyl; hydroxyC<sub>1-6</sub>alkylC<sub>2-</sub>

alkynyl; aminoC<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkylaminoC<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl; diC<sub>1-</sub>

alkylaminoC<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl; carboxyC<sub>1-6</sub>alkyl; or C<sub>1-6</sub>alkoxycarbonylaminoC<sub>1-8</sub>alkyl; heteroarylC<sub>1-6</sub>alkyl, wherein heteroaryl is *N*-containing monocyclic heteroaryl; or heterocycloalkylC<sub>1-6</sub>alkyl, wherein heterocycloalkyl is monocyclic heterocycloalkyl;

R<sup>4</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, cyano or C<sub>1-6</sub>alkoxy;

5 R<sup>5</sup> is hydrogen or C<sub>1-6</sub>alkyl;

R<sup>6</sup> is hydrogen; C<sub>1-6</sub>alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C<sub>3-7</sub>cycloalkyl, which is unsubstituted or once, twice or three times substituted by fluoro or C<sub>1-6</sub>alkyl; or phenyl-C<sub>x</sub>H<sub>2x</sub>-;

x is 1-6;

10 or a pharmaceutically acceptable salt, or enantiomer thereof.

3. The pharmaceutical composition according to claim 1 or 2, wherein the HBsAg inhibitor is (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

15 (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

20 (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

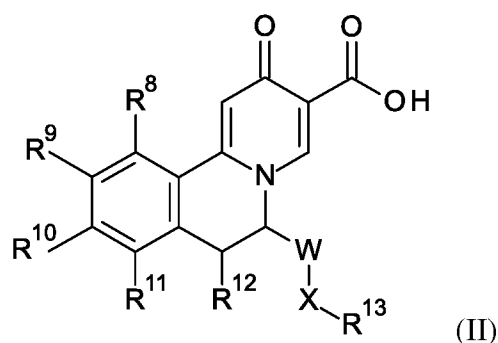
(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

25 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

4. The pharmaceutical composition according to claim 1, wherein the HBsAg inhibitor is a compound of formula (II):

-49-



wherein

$R^8$ ,  $R^9$ ,  $R^{10}$  and  $R^{11}$  are independently selected from hydrogen, halogen,  $C_{1-6}$ alkyl, di $C_{1-6}$ alkylamino, cyano, *N*-containing monocyclic heterocycloalkyl and  $OR^{14}$ , wherein

- 5  $R^{14}$  is hydrogen;  $C_{1-6}$ alkyl; or  $C_{1-6}$ alkyl which is substituted once or more times by fluoro,  $C_{3-7}$ cycloalkyl, phenyl, hydroxyl, amino,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkylsulfanyl,  $C_{1-6}$ alkylsulfonyl, di $C_{1-6}$ alkylamino,  $C_{1-6}$ alkoxycarbonylamino, monocyclic heterocycloalkyl, pyrazoyl or imidazolyl;

$R^{12}$  is hydrogen or  $C_{1-6}$ alkyl;

- 10  $R^{13}$  is hydrogen,  $C_{1-6}$ alkyl, phenyl- $C_xH_{2x-}$ ,  $C_{1-6}$ alkylcarbonyl,  $C_{1-6}$ alkylsulfonyl, benzoyl or monocyclic heterocycloalkyl, wherein  
x is 1-6;

W is a bond,  $C_yH_{2y}C(R^{15})(R^{16})C_zH_{2z}$  or  $C_yH_{2y}CH(R^{15})CH(R^{16})C_zH_{2z}$ , wherein  
 $R^{15}$  and  $R^{16}$  are independently selected from hydrogen, fluoro, hydroxy and  $C_{1-6}$ alkyl,  
15 y is 0-6;  
z is 0-6;

X is a bond; O; S;  $S(O)_2$ ; or  $NR^{17}$ , wherein  $R^{17}$  is hydrogen,  $C_{1-6}$ alkyl;  
or  $R^{13}$  and  $R^{17}$ , together with the nitrogen to which they are attached, form monocyclic  
heterocycloalkyl;

- 20 or a pharmaceutically acceptable salts, or enantiomers thereof.

5. The pharmaceutical composition according to claim 1 or 4, wherein the HBsAg inhibitor is  
(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-  
dihydrobenzo[a]quinolizine-3-carboxylic acid;

- (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-  
25 dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

5 (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

10 6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the nucleos(t)ide analogue is Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate; more particularly the nucleos(t)ide analogue is Entecavir.

15 7. The pharmaceutical composition according to any one of claims 1 to 6, wherein the interferon is a non-conjugated interferon alfa, a pegylated alfa-type interferon or a y-branched pegylated recombinant human interferon alpha-2b; particularly the interferon is Roferon A<sup>®</sup>, Intron A<sup>®</sup>, Pegasys<sup>®</sup>, PegIntron<sup>®</sup>, Pai Ge Bin or wIFN; more particularly the interferon is Pegasys<sup>®</sup> or wIFN.

20 8. The pharmaceutical composition according to claim 1, wherein the composition consists of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon, in a pharmaceutically acceptable carrier.

9. The pharmaceutical composition according to claim 1 or 8, wherein the composition consists of

25 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

30 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

5 (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

10 (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

15 (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

20 (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

25 (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

30 (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys®;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron®;

5 (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

10 (+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A®;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A®;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys®;

15 (+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron®;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

20 (+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A®;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A®;

25 (-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys®;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron®;

30 (-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

5 (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

10 (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

15 (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

20 (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

25 (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

30 (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

5 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

10 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

15 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

20 (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron<sup>®</sup>;

25 (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;

30 (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Roferon A<sup>®</sup>;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Intron A<sup>®</sup>;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys®;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegintron®;

5        (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pai Ge Bin; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN

in a pharmaceutically acceptable carrier.

10    10.    The pharmaceutical composition according to claim 1 or 8, wherein the composition consists of

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys®; or

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

15    dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN;  
in a pharmaceutically acceptable carrier.

11.    A method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon are used in the medicament.

20    12.    The method according to claim 11, wherein the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon are co-administered in the same formulation or different formulation.

13.    The method according to claim 11 or 12, wherein the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon are intended for administration to a subject by the same route or different routes.

25    14.    The method according to any one of claims 11 to 13, wherein the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon are intended for administration to a subject by parenteral or oral administration.

15.    The method according to any one of claims 11 to 14, wherein the administration is simultaneous or sequential.

16. The method according to any one of claims 11 to 15, wherein the HBsAg inhibitor is a compound of formula (I) or formula (II), or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

17. The method according to any one of claims 11 to 16, wherein the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-

3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid); or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid);

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

18. The method according to any one of claims 11 to 17, wherein the nucleos(t)ide analogue is Lamivudine; Adefovir dipivoxil, Entecavir, Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate. Particularly the nucleos(t)ide analogue is Entecavir.

19. The method according to any one of claims 11 to 18, wherein the interferon is a non-conjugated interferon alfa, a pegylated alfa-type interferon or a y-branched pegylated recombinant human interferon alpha-2b; particularly the interferon is Roferon A<sup>®</sup>, Intron A<sup>®</sup>, Pegasys<sup>®</sup>, PegIntron<sup>®</sup>, Pai Ge Bin or wIFN; more particularly the interferon is Pegasys<sup>®</sup> or wIFN.

5

20. The method according to any one of claims 11 to 19, wherein the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon used in the medicament are

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>; or

10 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN.

21. A kit comprising a container comprising an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon.

22. The kit according to claim 21, further comprising a sterile diluent.

15 23. The kit according to claim 21 or 22, further comprising a package insert comprising printed instructions directing the use of a combined treatment of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon as a method for treatment or prophylaxis of hepatitis B virus infection.

24. The kit according to any one of claims 21 to 23, wherein the HBsAg inhibitor is

20 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

25 (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

30 (-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

5 (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid); or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

25. The kit according to any one of claims 21 to 24, wherein the nucleos(t)ide analogue is  
15 Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate. Particularly the nucleos(t)ide analogue is Entecavir.

26. The kit according to any one of claims 21 to 25, wherein the interferon is a non-conjugated  
interferon alfa, a pegylated alfa-type interferon or a y-branched pegylated recombinant human  
interferon alpha-2b; particularly the interferon is Roferon A<sup>®</sup>, Intron A<sup>®</sup>, Pegasys<sup>®</sup>, PegIntron<sup>®</sup>,  
20 Pai Ge Bin or wIFN; more particularly the interferon is Pegasys<sup>®</sup> or wIFN.

27. The kit according to any one of claims 21 to 26, wherein the HBsAg inhibitor, the  
nucleos(t)ide analogue and the interferon used in the container are

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>; or

25 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN.

28. A method for the treatment or prophylaxis of hepatitis B virus infection, comprising  
administration to a subject with an effective amount of an HBsAg inhibitor, or a  
pharmaceutically acceptable salt, enantiomer or diastereomer thereof; an effective amount of a  
30 nucleos(t)ide analogue and an effective amount of an interferon.

29. The method according to claim 28, wherein the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-

5 dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

10 (+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

15 dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

20 (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

dihydrobenzo[a]quinolizine-3-carboxylic acid); or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-

25 dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

30. The method according to claim 28 or 29, wherein the nucleos(t)ide analogue is Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, Clevudine, Tenofovir disoproxil or Tenofovir disoproxil fumarate. Particularly the nucleos(t)ide analogue is Entecavir.

30 31. The method according to any one of claims 28 to 30, wherein the interferon is a non-conjugated interferon alfa, a pegylated alfa-type interferon or a y-branched pegylated recombinant human interferon alpha-2b; particularly the interferon is Roferon A<sup>®</sup>, Intron A<sup>®</sup>,

Pegasys<sup>®</sup>, PegIntron<sup>®</sup>, Pai Ge Bin or wIFN; more particularly the interferon is Pegasys<sup>®</sup> or wIFN.

32. The method according to any one of claims 28 to 31, wherein the HBsAg inhibitor, the nucleos(t)ide analogue and the interferon used are

- 5 (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and Pegasys<sup>®</sup>; or  
(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, Entecavir and wIFN.

33. The use of pharmaceutical composition according to any one of claims 1 to 10 as an  
10 antiviral medicament, in particular as the medicament for treatment or prophylaxis of hepatitis B virus infection.

34. The use of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon for the manufacture of pharmaceutical composition according to any one of claims 1 to 10 as an  
15 antiviral medicament, in particular the medicament for treatment or prophylaxis of hepatitis B virus infection.

35. The invention as hereinbefore described.

# Combination therapy of an HBsAg inhibitor, a nucleos(t)ide analogue and an interferon

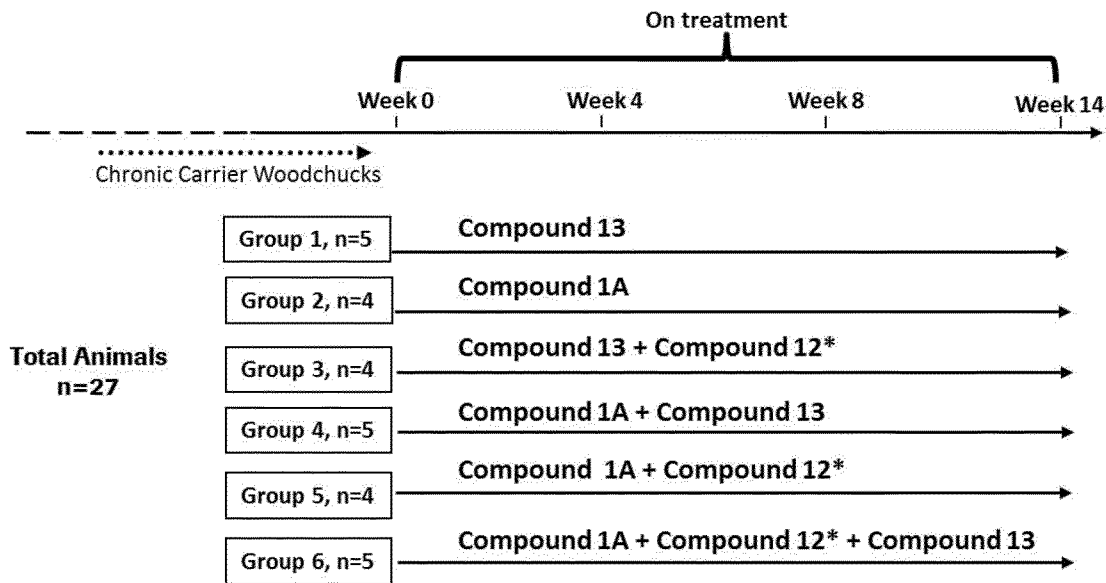


Figure 1

5

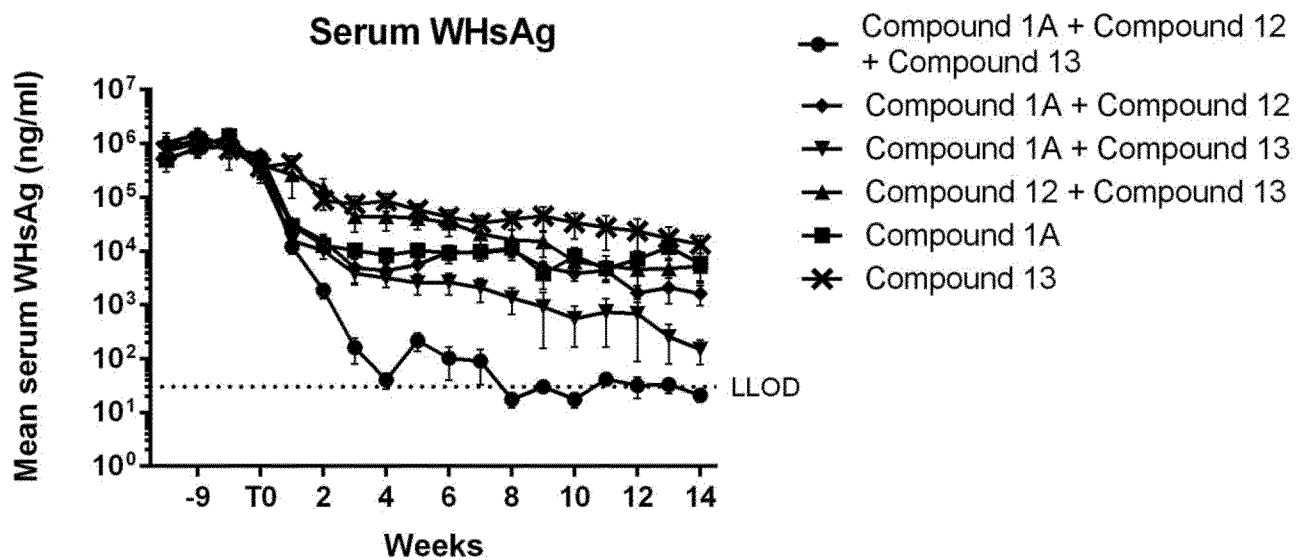


Figure 2

10

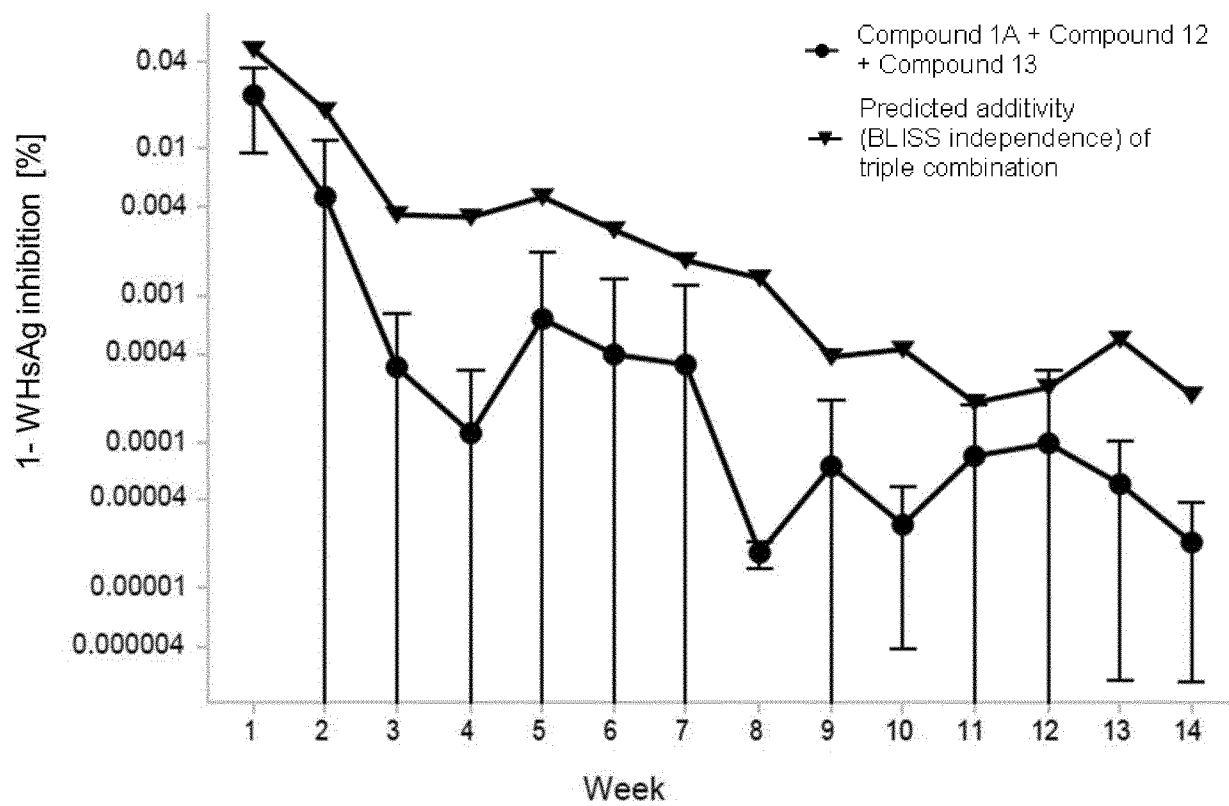


Figure 3

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/078974

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K38/21 A61K31/4745 A61K31/522 A61P31/20  
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, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No.                                                |
|-----------|------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| X         | CN 1 504 237 A (LAI QINGLIAN [CN])<br>16 June 2004 (2004-06-16)                    | 1,6-8,<br>11-15,<br>18,19,<br>21-23,<br>25,26,<br>28,30,<br>31,33-35 |
| Y         | claims 1-10; example 1<br>abstract<br><br>-----<br>-/--                            | 2-5,9,<br>10,16,<br>17,20,<br>24,27,<br>29,32                        |



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

22 January 2018

Date of mailing of the international search report

07/03/2018

Name and mailing address of the ISA/

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Renard, Delphine

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/078974

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                            | Relevant to claim No.                  |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| X         | WO 2015/113990 A1 (HOFFMANN LA ROCHE [CH];<br>HOFFMANN LA ROCHE [US])<br>6 August 2015 (2015-08-06)<br>cited in the application                                               | 1-35                                   |
| Y         | claims 1-32<br>page 47, lines 15-23                                                                                                                                           | 2,3,9,<br>10,17,<br>20,24,<br>27,29,32 |
| Y         | -----<br>WO 2016/071215 A1 (HOFFMANN LA ROCHE [CH];<br>HOFFMANN LA ROCHE [US])<br>12 May 2016 (2016-05-12)<br>cited in the application<br>claims 1-29                         | 4,5,9,<br>17,24,29                     |
| Y,P       | -----<br>WO 2017/114812 A1 (F HOFFMANN-LA ROCHE AG<br>[CH]; HOFFMANN-LA ROCHE INC [US])<br>6 July 2017 (2017-07-06)<br>the whole document<br>example 5                        | 1-35                                   |
| Y,P       | -----<br>WO 2017/102648 A1 (F HOFFMANN-LA ROCHE AG<br>[CH]; HOFFMANN-LA ROCHE INC [US])<br>22 June 2017 (2017-06-22)<br>figures 1-2; example 5<br>the whole document<br>----- | 1-35                                   |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/078974

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------|---------------------|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CN 1504237                                | A                   | 16-06-2004                 | NONE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| WO 2015113990                             | A1                  | 06-08-2015                 | AU 2015212903 A1 19-05-2016<br>CA 2931329 A1 06-08-2015<br>CL 2016001862 A1 20-01-2017<br>CN 105899508 A 24-08-2016<br>CR 20160241 A 15-07-2016<br>EA 201691261 A1 30-11-2016<br>EP 3099685 A1 07-12-2016<br>HK 1223931 A1 11-08-2017<br>JP 2017504633 A 09-02-2017<br>PE 06862016 A1 23-07-2016<br>PH 12016501254 A1 15-08-2016<br>SG 11201605970Q A 30-08-2016<br>TW 201540715 A 01-11-2015<br>US 2015210682 A1 30-07-2015<br>US 2016296515 A1 13-10-2016<br>WO 2015113990 A1 06-08-2015 |
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| WO 2017114812                             | A1                  | 06-07-2017                 | NONE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| WO 2017102648                             | A1                  | 22-06-2017                 | NONE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |