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Señor Jefe

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Santafé de Bogotá, D.C.

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2013. 2014. 2015. 2016. 2017. 2018. 2019. 2020. 2021. 2022. 2023. 2024. 2025. 2026. 2027. 2028. 2029. 2030. 2031. 2032. 2033. 2034. 2035. 2036. 2037. 2038. 2039. 2040. 2041. 2042. 2043. 2044. 2045. 2046. 2047. 2048. 2049. 2050. 2051. 2052. 2053. 2054. 2055. 2056. 2057. 2058. 2059. 2060. 2061. 2062. 2063. 2064. 2065. 2066. 2067. 2068. 2069. 2070. 2071. 2072. 2073. 2074. 2075. 2076. 2077. 2078. 2079. 2080. 2081. 2082. 2083. 2084. 2085. 2086. 2087. 2088. 2089. 2090. 2091. 2092. 2093. 2094. 2095. 2096. 2097. 2098. 2099. 2100. 2101. 2102. 2103. 2104. 2105. 2106. 2107. 2108. 2109. 2110. 2111. 2112. 2113. 2114. 2115. 2116. 2117. 2118. 2119. 2120. 2121. 2122. 2123. 2124. 2125. 2126. 2127. 2128. 2129. 2130. 2131. 2132. 2133. 2134. 2135. 2136. 2137. 2138. 2139. 2140. 2141. 2142. 2143. 2144. 2145. 2146. 2147. 2148. 2149. 2150. 2151. 2152. 2153. 2154. 2155. 2156. 2157. 2158. 2159. 2160. 2161. 2162. 2163. 2164. 2165. 2166. 2167. 2168. 2169. 2170. 2171. 2172. 2173. 2174. 2175. 2176. 2177. 2178. 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Request for grant of a

Patent

Form 1/77

Patents Act 1977

① Title of invention

- 1 Please give the title of the invention

NOVEL TREATMENT

② Applicant's details

- ☐ First or only applicant

- 2a If you are applying as a corporate body please give:
Corporate Name SmithKline Beecham Biologicals s.a.

Country (and State of incorporation, if appropriate) Belgium

- 2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

- 2c In all cases, please give the following details:

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B-1330 Rixensart, Belgium

UK postcode
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Country Belgium
ADP number 5800974002
(if known)

578 117001

4 Reference number	
4. Agent's or applicant's reference number <i>(if applicable)</i>	FB/RH/B45166

5 Claiming an earlier application date

5. Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Yes ☐ No ☒ ➔ go to 6

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☐ number of earlier application or patent number

☐ filing date (day month year)

☐ and the Section of the Patents Act 1977 under which you are claiming:

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

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⑥ Declaration of priority

6. If you are declaring priority from previous application(s), please give:		
Country of Filing	Priority application number (if known)	Filing Date (day, month, year)

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- any applicant is not an inventor
- there is an inventor who is not
 - an applicant, or
 - any applicant is a corporate body.

- 8 Please supply duplicates of claim(s), abstract, description and drawings).

Please mark correct box(es)

- 9 You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

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A completed fee sheet should preferably accompany the fee.

7 Inventorship

7. Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐

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A Statement of Inventorship on Patents form 7/77 will need to be filed (see Rule 15).).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application

Continuation sheets for this Patents Form 1/77

Claim(s)

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Description

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Abstract

Drawing(s)

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority documents (please state how many)

Patents Form 7/77 - Statement of Inventorship and Right to Grant

Patents Form 9/77 - Preliminary Examination Report

Patents Form 10/77 - Request for Substantive Examination

9 Request

I/We request the grant of a patent on the basis of this application.

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A W R TYRRELL

Date: 08/01/99

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Chartered Patent Attorney
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NOVEL TREATMENT

This invention relates to the use of a nucleoside analogue active against hepatitis B virus (HBV), or another class of antiviral active against HBV, such as α interferon or a nucleotide analogue and an HBV vaccine in the treatment of hepatitis B virus infections.

Chronic hepatitis B virus (HBV) infection, for which there is currently no effective cure, constitutes a global public health problem of enormous dimensions. Chronic carriers of HBV, estimated to number more than 300 million world-wide, are at risk for development of chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma.

EP-A-388049 (Beecham Group p.l.c.), discloses the use of penciclovir/famciclovir in the treatment of hepatitis B virus infection. All references herein to penciclovir/famciclovir include pharmaceutically acceptable salts, such as the hydrochloride, and solvates, such as hydrates.

EP-A-494119 (IAF Biochem. International Inc.) discloses the use of 1,3-oxathiolane nucleoside analogues, including lamivudine, in treatment of Hepatitis B.

The present invention provides a pharmaceutical pack comprising as active ingredients (1) an antiviral agent active against hepatitis B virus and (2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection, the active ingredients being for simultaneous or sequential use.

By pharmaceutical pack is meant a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Where the antiviral agent and the HBV vaccine are intended for administration as two separate compositions these may be presented in the form of, for example, a twin pack.

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The invention may be used for either the treatment or prophylaxis of hepatitis B infections. The invention is most particularly of value for treatment, for example, of chronic hepatitis B infections.

5 In one aspect, the antiviral agent as used in the pharmaceutical pack is a nucleoside agent. In a further aspect the antiviral agent is a nucleotide agent. Suitable agents for use in the invention include penciclovir, famciclovir, lamivudine, ganciclovir, lobucavir, adefovir, ribavirin, BMS200,475, vidarabin or ARA-AMP. Preferred nucleoside analogues include penciclovir, famciclovir and lamivudine.

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A further potential antiviral agent is an interferon. Alpha – interferon is especially preferred.

Information with respect to structure and activity of nucleoside analogues may be obtained from well known pharmaceutical industry references, such as "Pharmaprojects", PJB
15 publications Limited, Richmond, Surrey, U.K. or from 'R & D Focus', issued by IMS World publications, 364 Euston Road, London NW1 3BL.

References to an anti-hepatitis B virus nucleoside analogue, including the specific compounds mentioned hereinbefore and salts thereof, include solvates such as hydrates.

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Examples of pharmaceutically acceptable salts are as described in the aforementioned Patent reference in the name of Beecham Group p.l.c. and references quoted therein, the subject matter of which are incorporated herein by reference.

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It will be appreciated that the anti-hepatitis B virus nucleoside or nucleotide analogue and HBV vaccine of this invention may be administered in combination with other pharmacologically active agents, in particular, other antivirals.

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In this invention the vaccine for the prophylaxis and/or treatment of hepatitis B infection includes all vaccines containing HBV antigens (such as surface antigen, core and polymerase) and therapeutic vaccines.

In one aspect of the invention the hepatitis B virus antigen is the hepatitis B surface antigen (HBsAg). The preparation of Hepatitis B surface antigen is well documented. See for example, Harford et. al. in Develop. Biol. Standard 54, page 125 (1983), Gregg et. al. in Biotechnology, 5, page 479 (1987), EP-A- 0 226 846, EP-A-0 299 108 and references therein.

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As used herein the expression 'Hepatitis B surface antigen' or 'HBsAg' includes any HBsAg antigen or fragment thereof displaying the antigenicity of HBV surface antigen. It will be understood that in addition to the 226 amino acid sequence of the HBsAg S antigen (see Tiollais et. al. Nature, 317, 489 (1985) and references therein) HBsAg as herein described may, if desired, contain all or part of a pre-S sequence as described in the above references and in EP-A- 0 278 940. HBsAg as herein described can also refer to variants, for example the 'escape mutant' described in WO 91/14703. In a further aspect the HBsAg may comprise a protein described as L* in European Patent Application Number 0 414 374, that is to say a protein, the amino acid sequence of which consists of parts of the amino acid sequence of the hepatitis B virus large (L) protein (ad or ay subtype), characterised in that the amino acid sequence of the protein consists of either:

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(a) residues 12 - 52, followed by residues 133 - 145, followed by residues 175 - 400 of the said L protein; or

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(b) residue 12, followed by residues 14 - 52, followed by residues 133 - 145, followed by residues 175 - 400 of the said L protein.

HBsAg may also refer to polypeptides described in EP 0 198 474 or EP 0 304 578.

Normally the HBsAg will be in particle form. It may comprise S protein alone or may be as composite particles, for example (S, L*) wherein L* is as defined above and S denotes the S-protein of hepatitis B surface antigen.

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The preferred hepatitis B antigen is this composite particle, defined as S,L*.

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Such a vaccine may advantageously include a pharmaceutically acceptable excipient such as a suitable adjuvant. Suitable adjuvants include an aluminium salt such as aluminium hydroxide gel (alum) or aluminium phosphate (as described in WO93/24148), but may also be a salt of calcium, iron or zinc, or may be an insoluble suspension of acylated tyrosine, or acylated sugars, cationically or anionically derivatised polysaccharides, or polyphosphazenes.

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Advantageously, the hepatitis B virus may be formulated with strong adjuvant systems. Thus in the formulation of the invention, it is preferred that the adjuvant composition induces an immune response comprising TH1 aspects. Suitable adjuvant systems include, for example a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL) together with an aluminium salts. A vaccine comprising hepatitis B surface antigen in conjunction with 3D-MPL was described in European Patent Application 0 633 784.

An enhanced system involves the combination of monophosphoryl lipid A and a saponin derivative particularly the combination of QS21 and 3D-MPL as disclosed in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol as disclosed in WO 96/33739.

Other known adjuvants which may be included are CpG containing oligonucleotides (see University of Iowa; WO9602555).

In a preferred embodiment of the present invention there is provided a vaccine comprising an HBV antigen, adjuvanted with a monophosphoryl lipid A or derivative thereof.

Preferably the vaccine additionally comprises a saponin, more preferably QS21.

Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

A particularly potent adjuvant formulation involving QS21, 3D-MPL & tocopherol in an oil in water emulsion is described in WO 95/17210.

The present invention also provides a method of treatment and/or prophylaxis of hepatitis B virus infections, which comprises administering to a human or animal subject, suffering from or susceptible to Hepatitis B virus infection, either either simultaneously or sequentially in any order, a safe and effective amount of 1) an antiviral agent active against hepatitis B virus and 2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection.

The antiviral such as penciclovir/famciclovir and the HBV vaccine or a pharmaceutically acceptable salt or ester thereof, may be co-administered in the form of two separate pharmaceutical compositions for simultaneous or sequential use. Normally the active ingredients will be administered separately according to the normal dosage and administration regimen for the ingredients given alone. Commencement of administration may be either with the vaccine or the antiviral.

The present invention also provides for the use of an antiviral compound in the manufacture of a medicament for the treatment of patients already primed with a hepatitis B vaccine and suffering from a hepatitis B virus infection. The invention further provides for the use of a hepatitis B vaccine in the manufacture of a medicament for the treatment of patients already primed with an antiviral compound and suffering from a hepatitis B virus infection. The preferred antiviral is a nucleoside analogue, most preferably penciclovir/famciclovir or lamivudine. Preferred hepatitis B vaccines are identified hereinabove.

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The unit doses of the nucleoside or nucleotide analogue may be administered, for example, 1 to 4 times per day. The exact dose will depend on the route of administration and the severity of the condition being treated, and it will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient and immunocompromised patients may require an increased dosage.

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Vaccines are administered in multiple doses at various intervals. This is usually 6 - 12 doses at biweekly or monthly intervals.

The preferred ingredients in the pharmaceutical pack when administered simultaneously are given as separate preparations, for example, as vaccinations in each arm. It is however possible to consider simultaneous administration by mixing the ingredients before administration. The ingredients may be given enterally, such as orally or parenterally (e.g. intramuscularly or, more particularly, intravenously).

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The antiviral agents of the invention may be formulated as a tablet prepared by conventional means. Compositions for oral use such as tablets and capsules may be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, micro-crystalline cellulose or calcium hydrogen phosphate); lubricant (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agent (e.g. sodium lauryl sulphate). Tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of one or both active ingredients.

For parenteral administration the compositions may be presented in a form suitable for bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in syringes, ampoules or in multi-dose containers, with an added preservative.

The active antiviral agent may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredients may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For rectal administration the active antiviral agents may be formulated as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The active antiviral agents of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the penciclovir/famciclovir may be admixed, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

Anti-hepatitis B virus nucleoside analogues may be identified by standard methods, such as tests involving studies in *in vitro* primary duck hepatocyte cultures infected with the duck hepatitis B virus (DHBV). Changes in the levels of preS1 and/or viral DNA in cultures treated with such analogs would indicate activity. Alternatively, analogues may be identified by the ability to interfere with normal acylation of synthetic peptides representing the N-terminal amino acids of DHBV or hepatitis B viruses of man, woodchucks, ground squirrels or other animals.

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45**WHAT IS CLAIMED IS:**

1. A pharmaceutical pack comprising as active ingredients (1) an antiviral agent active
5 against hepatitis B virus and (2) a vaccine for the prophylaxis and/or treatment of hepatitis
B infection, the active ingredients being for simultaneous or sequential use.
2. A pharmaceutical pack as claimed in claim 1 for use in the treatment of hepatitis B
infections.
- 10 3. A pharmaceutical pack as claimed in claim 1 for use in the prevention of hepatitis B
infections.
4. A pharmaceutical pack as claimed in any one of the preceding claims wherein the antiviral
15 agent is a nucleoside analogue.
5. A pharmaceutical pack as claimed in claim 4 wherein the antiviral agent is selected from
the group comprising; penciclovir, famciclovir or lamivudine.
- 20 6. A pharmaceutical pack as claimed in any one of claims 1 – 3 wherein the antiviral agent is
a nucleotide analogue.
7. A pharmaceutical pack as claimed in claim 4 or claim 6 wherein the antiviral agent is
selected from the group comprising; ganciclovir, lobucavir, adefovir, ribavirin,
25 BMS200,475, vidarabin or ARA-AMP.
8. A pharmaceutical pack as claimed in any one of claims 1 – 3 wherein the antiviral agent is
alpha - interferon.
- 30 9. A pharmaceutical pack as claimed in any one of the preceding claims wherein the vaccine
active against hepatitis B comprises hepatitis B surface antigen.

10. A pharmaceutical pack as claimed in claim 9 wherein the vaccine active against hepatitis B comprises the antigen SL*.

5 11. A pharmaceutical pack as claimed in any one of the preceding claims in which the vaccine comprises an adjuvant.

10 12. A pharmaceutical pack as claimed in claim 11 wherein the adjuvant is selected from the group of adjuvants comprising: 3D-MPL, QS21, a mixture of QS21 and cholesterol, a CpG oligonucleotide, aluminium hydroxide, aluminium phosphate and tocopherol, a water in oil emulsion and an oil in water emulsion or a combination of two or more of the said adjuvants.

15 13. A method of treating a patient suffering from or susceptible to Hepatitis B virus infection, comprising administering to a patient in need thereof, either simultaneously or sequentially in any order, a safe and effective amount of 1) an antiviral agent active against hepatitis B virus and 2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection.

14. A method as claimed in claim 13 which comprises the use of a pharmaceutical pack according to any of claims 1 to 11.

20 15. Use of an antiviral compound in the manufacture of a medicament for the treatment of patients already primed with a hepatitis B vaccine and suffering from a hepatitis B virus infection.

25 16. Use of a hepatitis B vaccine in the manufacture of a medicament for the treatment of patients already primed with an antiviral compound and suffering from a hepatitis B virus infection.

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LEGALIZACIONES

OFICINA DE PATENTES

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras “sociedad anónima” o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras “sociedad anónima” (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW CRESSEY

FECHA: 13 de diciembre de 1999

(SELLO DE LACRE)

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OFICINA DE PATENTES

Referencia No. **FB/RH/B45166** No. **9900630.6** 12 de enero de 1999

OFICINA DE PATENTES: Solicitud de adjudicación de una Patente.

Forma 1/77

Ley de Patentes de 1977

1. TITULO DEL INVENTO: "TRATAMIENTO NOVEDOSOS"

2. INFORMACIÓN DEL SOLICITANTE:

2a. Nombre: SmithKline Beecham Biologicals S.A.

Pais: Bélgica

2b N/A

2c Dirección: Rue de l'Institut 89
B-1330 Rixensart
Bélgica

Código Postal:

PAIS. BELGICA

ADP No. **5781117001**

2d **Segundo Solicitante:**

N/A

3. Ha nombrado Ud. a alguien que le represente en su solicitud? SI

Nombre del Agente: A W R TYRRELL

SmithKline Beecham

Corporate Intellectual Property

Two New Horizons Court,

Brentford, Middlesex

Código postal TW8 9EP

No. ADP

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12
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4. Número de Referencia: **FB/RH/B45166**
 5. Solicita Ud. que esta solicitud sea tratada como si hubiera sido radicada en la fecha de presentación de una solicitud anterior: NO
 6. No aplica
 7. Es usted el único inventor o inventor conjunto? NO
 8. Cuántas hojas describen esta solicitud? 07 - Reivindicaciones: 2-

Resumen: 1- - Dibujos - -

9. Solicitud: Solicitamos la adjudicación de una patente teniendo en cuenta esta solicitud.

(FIRMA) A W R TYRRELL

Fecha: 08/01/99

Abogado de Patentes

Favor devolver la forma diligenciada y sus anexos y duplicados, junto con su valor a:

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TRATAMIENTO NOVEDOSO

REIVINDICACIONES:

1. Un paquete farmacéutico que comprende como ingredientes activos (1) un agente antiviral activo contra el virus de hepatitis B, y (2) una vacuna para la profilaxis y/o tratamiento de infección de hepatitis B; los ingredientes activos son para uso simultáneo o secuencial.
2. Un paquete farmacéutico según la reivindicación 1, para uso en el tratamiento de infecciones de Hepatitis B.
3. Un paquete farmacéutico según la reivindicación 1, para uso en la prevención de infecciones de Hepatitis B.
4. Un paquete farmacéutico según cualquiera de las reivindicaciones anteriores en donde el agente antiviral es un análogo nucleósido.
5. Un paquete farmacéutico según la reivindicación 4, en donde el agente antiviral es seleccionado del grupo consistente de; penciclovir, famciclovir o lamivudine.
6. Un paquete farmacéutico según cualquiera de las reivindicaciones 1 a 3, en donde el agente antiviral es un análogo nucleótido.
7. Un paquete farmacéutico según la reivindicación 4 ó 6, en donde el agente antiviral es seleccionado del grupo consistente de: ganciclovir, lobucavir, adefovir, ribavirin, BMS200,475, vidarabin o ARA-AMP.
8. Un paquete farmacéutico según cualquiera de las reivindicaciones 1 a 3, en donde el agente antiviral es alfa-interferon.

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9. Un paquete farmacéutico según cualquiera de las reivindicaciones anteriores, en donde la vacuna activa contra hepatitis B comprende antígeno de superficie de Hepatitis B.
 10. Un paquete farmacéutico según la reivindicación en donde la vacuna activa contra hepatitis B comprende el antígeno SL*.
 11. Un paquete farmacéutico según cualquiera de las reivindicaciones anteriores, en el cual la vacuna comprende un adyuvante.
 12. Un paquete farmacéutico según la reivindicación 11, en donde el adyuvante es seleccionado del grupo de adyuvantes que comprende: 3D-MPL, QS21, una mezcla de QS21 y colesterol, un oligonucleótido CpG, hidróxido de aluminio, fosfato de aluminio y tocoferol, una emulsión agua en aceite, y una emulsión aceite en agua, o una combinación de dos o más de dichos adyuvantes.
 13. Un método para tratar a un paciente que sufre de, o que sea susceptible de infección del virus de Hepatitis B, que comprende administrar a un paciente que lo requiera, bien sea simultáneamente o secuencialmente en cualquier orden, una cantidad segura y efectiva de (1) un agente antiviral activo contra el virus de Hepatitis B, y (2) una vacuna para la profilaxis y/o tratamiento de infección de Hepatitis B.
 14. Un método según la reivindicación 13, que comprende el uso de un paquete farmacéutico según cualquiera de las reivindicaciones 1 a 11.
 15. Uso de un compuesto antiviral en la fabricación de un medicamento para el tratamiento de pacientes ya iniciados con vacuna de Hepatitis B y que sufren de una infección del virus de Hepatitis B.

16. Uso de una vacuna de Hepatitis B en la fabricación de un medicamento para el tratamiento de pacientes ya iniciados con un compuesto antiviral y que sufren de una infección del virus de Hepatitis B.