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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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División de Nuevas Creaciones

PCT  
SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

04-100434

54. TITULO FORMULACIONES LIQUIDAS DE BAJA DOSIS DE ENTECAVIR Y SU USO

51. CLASIFICACION INTERNACIONAL A61K9/30/A61K31/52

71. SOLICITANTE BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO PRINCETON. NEW JERSEY. ESTADOS UNIDOS DE AMERICA

74. APODERADO RAMIRO CASTRO DUQUE

22. SANTAFE DE BOGOTA, D.C.

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

## FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

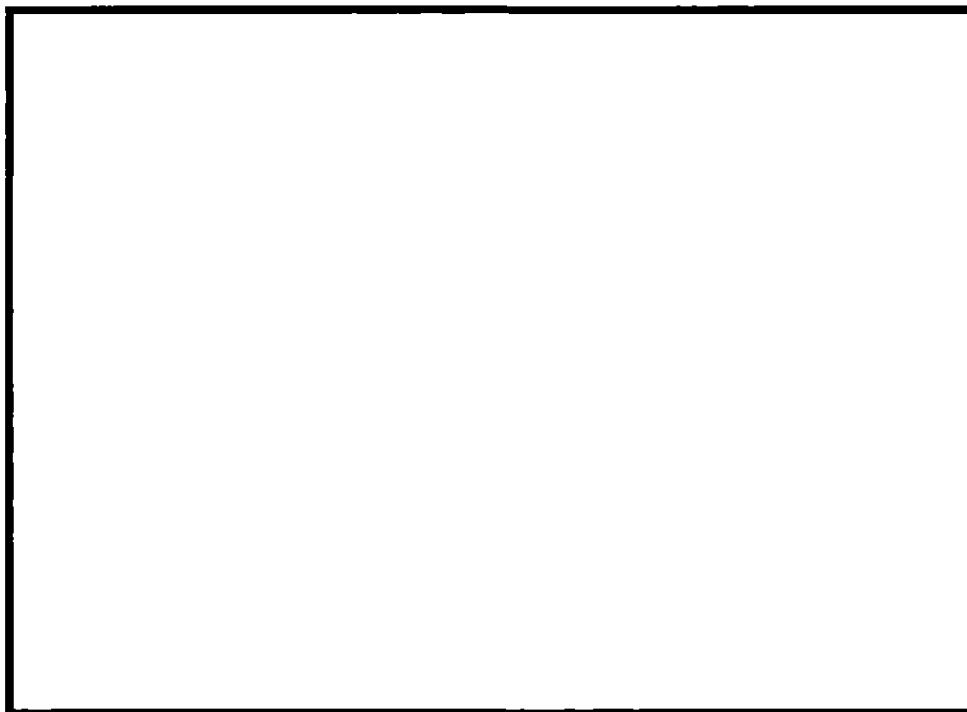
|                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                 |                                                         |                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 SOLICITUD DE:                                                                                                                                                         |                                                                                                                                                                                                                                                                                                 |                                                         |                                                                                                                                                                                                |
| <input checked="" type="checkbox"/> Patente de Invención.                                                                                                               |                                                                                                                                                                                                                                                                                                 | <input type="checkbox"/> Patente de Modelo de Utilidad. |                                                                                                                                                                                                |
| <input type="checkbox"/> Capítulo I.                                                                                                                                    |                                                                                                                                                                                                                                                                                                 | <input checked="" type="checkbox"/> Capítulo II.        |                                                                                                                                                                                                |
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| Título (54): <u>FORMULACIONES LÍQUIDAS DE BAJA DOSIS DE ENTECAVIR Y SU USO</u>                                                                                          |                                                                                                                                                                                                                                                                                                 |                                                         |                                                                                                                                                                                                |
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| Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.                                                                             |                                                                                                                                                                                                                                                                                                 |                                                         |                                                                                                                                                                                                |

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$422.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Protocolo No. 19358
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá F.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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##### CONSIGNACION #####

| DEPOSITANTE           | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PAGO | Vr. PAGO      |
|-----------------------|--------------|---------------|-------------|----------|------------|---------------|
| BRIGARD & CASTRO LTDA | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 21591344 | 10/09/2004 | 17,220,000.00 |

##### CONCEPTO #####

| CANT. CONTABILITICO       | CONCEPTO                            | TOTAL CONCEPTO |
|---------------------------|-------------------------------------|----------------|
| 1 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 422,000.00     |
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LOW DOSE LIQUID ENTECAVIR FORMULATIONS AND USE

(57) Abstract: Liquid pharmaceutical compositions are provided having a low dose of entecavir. In one embodiment of the present invention, the liquid entecavir composition is a ready-to-use composition that is formulated to be both stable and palatable. In a second embodiment of the present invention, the liquid entecavir composition is formulated from a powder composition at the time of use. The low dose entecavir compositions may also include at least one component selected from sweetener, preservative, flavoring agent, buffering agent, or combinations thereof. The liquid entecavir compositions may also be formulated in combination with other pharmaceutically active agents.

WO 03/086367 A1

## LOW DOSE LIQUID ENTECAVIR FORMULATIONS AND USE

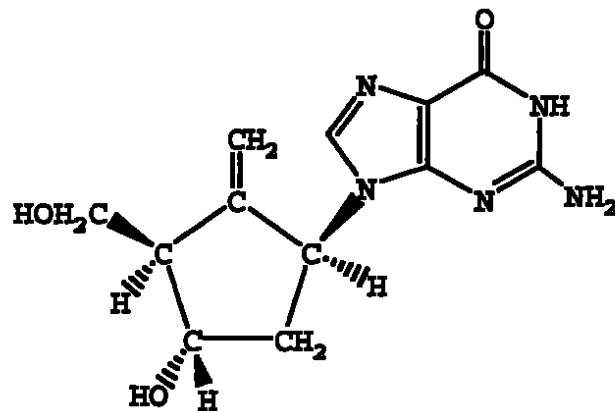
This application claims priority from Serial No. 60/370,674 filed April 8, 2002.

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### BACKGROUND OF THE INVENTION

Entecavir, [1S-(1 $\alpha$ ,3 $\alpha$ ,4 $\beta$ )]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one, having the chemical structure

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is an antiviral agent currently undergoing clinical evaluation for the treatment of hepatitis B virus (HBV) infection.

15 U.S. Patent No. 5,206,244 to Zahler et al., discloses entecavir and its use in treating hepatitis B. Zahler discloses that an effective antiviral dose for oral or parenteral administration will likely be in the range of about 1.0 to 50 mg/kg of body weight and that the desired dose may be administered several times daily at appropriate intervals.

20 Improved methods for the synthesis of entecavir are disclosed by Bisacchi et al. in WO 98/09964.

Low dose entecavir formulations, particularly tablets and capsules, are disclosed in U.S. application US-2001-0033864-A1 published October 25, 2001 and PCT application WO 01/64221 A1 published September 7, 2001.

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### SUMMARY OF THE INVENTION

It is an object of the present invention to provide a liquid pharmaceutical composition having a low dose of entecavir capable of safely and effectively treating hepatitis B virus infection.

5        It is another object of the present invention to provide such a low dose liquid entecavir composition that is ready-to-use.

It is still another object of the present invention to provide such a low dose liquid entecavir composition that is both stable and palatable.

10       It is yet another object of the present invention to provide such a low dose liquid entecavir composition that is formulated from a powder for constitution as a liquid composition at the time of use.

It is a further object of the present invention to provide a process for formulating a low dose, ready-to-use, liquid entecavir composition.

15       It is still a further object of the present invention to provide a process for formulating a low dose, liquid entecavir composition from a powder for constitution as a liquid composition at the time of use.

These and other objects and advantages of the present invention are accomplished by a liquid pharmaceutical composition having a low dose of entecavir. In one embodiment of the present invention, the liquid entecavir composition is a  
20       ready-to-use composition that is formulated to be both stable and palatable. In a second embodiment of the present invention, the liquid entecavir composition is formulated from a powder for constitution as a liquid composition at the time of use. The low dose entecavir compositions also have at least one additional component selected from one or more of the following: sweetener, preservative, flavoring agent,  
25       buffering agent, pH adjusting agent, or any combinations thereof. The liquid entecavir compositions may also be formulated in combination with other pharmaceutically active agents.

### DETAILED DESCRIPTION OF THE INVENTION

30       Entecavir is a potent antiviral agent, which has shown good efficacy against HBV. Since entecavir is very potent, very low doses are sufficient to achieve the desired therapeutic effects. However, low dose formulations, and notably liquid

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formulations, pose great challenges to formulators because the drug degrades faster in the liquid state than in the solid state. Any minor degradation translates into a significant reduction in potency.

While entecavir is potent, it is also extremely bitter. To combat the bitterness, a sweetener is generally used. However, entecavir has shown a tendency to react with commonly used sweeteners, such as sucrose, creating stability concerns. Entecavir has a primary amine group in its structure that has the propensity to react with any sweetener or flavoring agent that contains aldehyde and/or ketone groups. This reaction is more pronounced at a weakly acidic pH (pH 3 to 4), but minimized at pH 5 to 7.

This invention is directed to liquid pharmaceutical compositions containing a low dose of the active antiviral agent entecavir for once daily administration to treat hepatitis B virus infection in an adult human patient or a pediatric patient. The liquid pharmaceutical compositions also have at least one additional component selected from one or more of the following: sweetener, preservative, flavoring agent, buffering agent, pH adjusting agent, other pharmaceutically active agents particularly another antiviral agent, or any combinations thereof.

The term adult human patient is defined as a patient of about 16 years or more of age and a weight equal to or greater than about 50 kilograms. Pharmaceutical compositions containing entecavir at the lower end of the above ranges are suitable for administration to pediatric patients or adult patients weighing less than about 50 kilograms.

In one embodiment of the present invention, the liquid entecavir composition is a ready-to-use pharmaceutical composition. The concentration of each component present in the liquid entecavir composition is reflected in a percent weight by volume (%w/v). The antiviral agent entecavir is present in the liquid, ready-to-use pharmaceutical composition in an amount about 0.001% to about 20%. Preferably, the entecavir is present in the composition in an amount about 0.003% to about 10%, more preferably between about 0.005% and about 5%, and most preferably between about 0.005% and about 1%.

To counteract the bitterness associated with entecavir, and to make the composition palatable, a sweetener may be added to the composition. Suitable

sweeteners include, for example, maltitol (Lycasin®), sucrose, sorbitol, xylitol, mannitol, or any combinations thereof. The sweetener is present in the composition in an amount about 10% to about 85%. Preferably, sweetener is present in an amount about 15% to about 70%.

5           To further enhance the palatability of the entecavir composition of the present invention, a flavoring agent may be added to the composition. Suitable flavoring agents include, for example, cherry, guarana, orange, banana, strawberry, vanilla, chocolate, or any combinations thereof. The flavoring agent may be present in the composition in an amount about 0.001% to about 2%. Preferably, the flavoring agent  
10 is present in an amount about 0.01% to about 0.075%.

          The composition of the present invention may also include a preservative. Suitable preservatives include, for example, methylparaben, propylparaben, butylparaben, sodium benzoate, potassium sorbate, or any combinations thereof. The preservative may be present in the composition in an amount about 0.01% to about  
15 1.0%. Preferably, preservative is present in an amount about 0.1% to about 0.75%.

          The pH of the composition may be adjusted with any suitable dilute acid or base. By way of example, a suitable dilute acid is hydrochloric acid and a suitable dilute base is sodium hydroxide. The pH of the composition is preferably about 5 to about 7.

20           The inclusion of a buffering agent to maintain a composition pH of about 5 to about 7 is important both for the stability of the entecavir with the sweetener and the stability of the preservative. Suitable buffering agents include, for example, citric acid, sodium citrate, phosphate buffer, acetate buffer, or any combinations thereof. The buffering agent is present in the composition in an amount sufficient to maintain a  
25 composition pH of about 5 to about 7. Preferably, the molar concentration of the buffering agent is between about 5 mM to about 200 mM. The buffering agent is present in the composition in an amount about 0.01% to about 5%.

          The above components of the liquid entecavir composition may be formulated in solution with any suitable pharmaceutically acceptable solvent. A suitable  
30 pharmaceutically acceptable solvent includes, for example, water, PEG 400, propylene glycol, ethanol, glycerin, or any combinations thereof. Preferably, the pharmaceutically acceptable solvent is water.

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Two preferred, ready-to-use, liquid entecavir compositions of the present invention are set forth in Tables 1 and 2 below.

**TABLE 1**

5                      Ready to Use (RTU) Entecavir (0.2 mg/mL) Liquid Formulation

| Ingredients                    | Gram/100 ml                               | Function        |
|--------------------------------|-------------------------------------------|-----------------|
| Entecavir                      | 0.02                                      | Antiviral Agent |
| Maltitol (Lycasin®)            | 65.0                                      | Sweetener       |
| Methylparaben                  | 0.2                                       | Preservative    |
| Propylparaben                  | 0.028                                     | Preservative    |
| Cherry or Guarana<br>or Orange | 0.05/0.025/0.025                          | Flavoring Agent |
| Citric Acid/Sodium Citrate     | 0.96/1.47 (100mM) or<br>0.037/0.24 (10mM) | Buffering Agent |
| Water                          | q.s. to 100 mL (pH 6.0)                   | Solvent         |

**TABLE 2**

                    Ready to Use (RTU) Entecavir (0.05 mg/mL) Liquid Formulation

| Ingredients                    | Gram/100 ml                                 | Function        |
|--------------------------------|---------------------------------------------|-----------------|
| Entecavir                      | 0.005                                       | Antiviral Agent |
| Maltitol (Lycasin®)            | 65.0                                        | Sweetener       |
| Methylparaben                  | 0.2                                         | Preservative    |
| Propylparaben                  | 0.028                                       | Preservative    |
| Cherry or Guarana<br>or Orange | 0.05/0.025/0.025                            | Flavoring Agent |
| Citric Acid/Sodium Citrate     | 0.96/1.47 (100 mM) or<br>0.037/0.24 (10 mM) | Buffering Agent |
| Water                          | q.s. to 100 mL (pH 6.0)                     | Solvent         |

10                      The stability of the ready-to-use liquid entecavir compositions of the present invention is demonstrated below in Tables 3 and 4.

TABLE 3  
Stability of Entecavir Ready-to-Use (RTU) Liquid Formulation<sup>a</sup>, 0.05 mg/mL, in Clear Glass Bottles

| Time, weeks | Storage condition                 | Entecavir      |         | Impurity/Degradant, % I.I. |                   | Methylparaben  |         | Propylparaben  |         | pH/<br>Appearance |
|-------------|-----------------------------------|----------------|---------|----------------------------|-------------------|----------------|---------|----------------|---------|-------------------|
|             |                                   | Potency, mg/mL | % Label | RRT 0.24                   | Total             | Potency, mg/mL | % Label | Potency, mg/mL | % Label |                   |
| Initial     |                                   | 0.0508         | 101.6   | 0.07                       | 0.07              | 1.94           | 97      | 0.273          | 97.5    | 5.99/complies     |
| 4 days      | 25°C/HIL/UVA <sup>b</sup> , PROT  | 0.0506         | 101.2   | 0.07                       | 0.07              | 1.98           | 99      | 0.277          | 98.9    | 6.02/complies     |
|             | 25°C/HIL/UVA <sup>b</sup> , EXPOS | 0.0503         | 100.6   | 0.07                       | 0.07              | 1.98           | 99      | 0.278          | 99.3    | 6.03/complies     |
| 2           | 25°C/HIL/UVA <sup>b</sup> PROT    | 0.0506         | 101.2   | 0.07                       | 0.07              | 2.00           | 100     | 0.284          | 101.4   | 5.67/complies     |
|             | 25°C/HIL/UVA <sup>b</sup> EXPOS   | 0.0499         | 99.8    | 0.07                       | 0.74 <sup>c</sup> | 1.98           | 99.0    | 0.279          | 99.6    | 5.91/complies     |
|             | 30°C/60%RH                        | 0.0512         | 102.4   | 0.06                       | 0.06              | 2.0            | 100     | 0.281          | 100.4   | 6.02/complies     |
|             | 40°C/75%RH                        | 0.0513         | 102.6   | 0.09                       | 0.09              | 1.99           | 99.5    | 0.278          | 99.3    | 6.03/complies     |
| 4           | 30°C/60%RH                        | 0.0509         | 101.8   | 0.07                       | 0.07              | 1.97           | 98.5    | 0.280          | 100     | 6.03/complies     |
|             | 40°C/75%RH                        | 0.0509         | 101.8   | 0.07                       | 0.07              | 1.95           | 97.5    | 0.279          | 99.6    | 6.01/complies     |
|             | 50°C                              | 0.0505         | 101.0   | 0.08                       | 0.08              | 1.89           | 94.5    | 0.276          | 98.6    | 6.00/complies     |
| 13          | 25°C/60%RH                        | 0.0509         | 101.8   | 0.07                       | 0.07              | 2.00           | 100     | 0.286          | 102.1   | 6.03/complies     |
|             | 30°C/60%RH                        | 0.0515         | 103.0   | 0.07                       | 0.07              | 1.97           | 98.5    | 0.282          | 100.7   | 6.01/complies     |
|             | 40°C/75%RH                        | 0.0508         | 101.6   | 0.07                       | 0.07              | 1.91           | 95.5    | 0.281          | 100.4   | 6.00/complies     |
|             | 50°C                              | 0.0500         | 100.0   | 0.05                       | 0.05              | 1.73           | 86.5    | 0.272          | 97.1    | 5.99/complies     |
| 26          | 5°C                               | 0.0512         | 102.4   | <0.05                      | <0.05             | 2.00           | 100     | 0.284          | 101.4   | 5.99/complies     |
|             | 25°C/60%RH                        | 0.0509         | 101.8   | <0.05                      | <0.05             | 1.96           | 98      | 0.281          | 100.4   | 6.00/complies     |
|             | 30°C/60%RH                        | 0.0510         | 102     | <0.05                      | <0.05             | 1.94           | 97      | 0.280          | 100.0   | 5.99/complies     |
|             | 40°C/75%RH                        | 0.0501         | 100.2   | <0.05                      | <0.05             | 1.80           | 90      | 0.274          | 97.9    | 5.99/complies     |

<sup>a</sup> The solutions were stored in 4 oz (120 mL) glass bottles with child-resistant cap at 66-mL fill.  
The bottles were stored at an upright position except for photostability samples, where the bottles were stored lying on their side.  
<sup>b</sup> HIL/UVA = Ultraviolet-A (range 320-400 nm) and high-intensity visible fluorescent light.  
The ICH guidelines of 200 watt hours/m<sup>2</sup> and 1.2 x 10<sup>6</sup> lux hours are met after approximately 4 days.  
<sup>c</sup> Two additional degradants with RRT of 1.8 (0.61% I.I.) and 2.1 (0.05% I.I.) were detected in this sample.  
RH = relative humidity  
RRT = relative retention time  
PROT = protected (bottle has cap)  
EXPOS = unprotected (no cap)

TABLE 4  
Stability of Entecavir Ready-to-Use (RTU) Liquid Formulation<sup>a</sup>, 0.2 mg/mL, in Clear Glass Bottles

| Time, weeks | Storage condition   | Entecavir      |         | Impurity/Degradant, % I.I. |                   | Methylparaben  |                   | Propylparaben  |                   | pH/<br>Appearance |
|-------------|---------------------|----------------|---------|----------------------------|-------------------|----------------|-------------------|----------------|-------------------|-------------------|
|             |                     | Potency, mg/mL | % Label | RRT 0.24                   | Total             | Potency, mg/mL | % Label           | Potency, mg/mL | % Label           |                   |
| Initial     |                     | 0.204          | 102     | 0.07                       | 0.07              | 1.87           | 93.5 <sup>a</sup> | 0.264          | 94.3 <sup>a</sup> | 5.96/complies     |
| 4 days      | 25°C/HIL/UVAB PROT  | 0.201          | 100.5   | 0.07                       | 0.07              | 1.96           | 98                | 0.277          | 98.9              | 6.02/complies     |
|             | 25°C/HIL/UVAB EXPOS | 0.200          | 100     | 0.06                       | 0.06              | 1.95           | 97.5              | 0.275          | 98.2              | 6.04/complies     |
| 2           | 25°C/HIL/UVAB PROT  | 0.203          | 101.5   | 0.07                       | 0.07              | 1.99           | 99.5              | 0.282          | 100.7             | 5.75/complies     |
|             | 25°C/HIL/UVAB EXPOS | 0.199          | 99.5    | 0.07                       | 0.26 <sup>b</sup> | 1.97           | 98.5              | 0.278          | 99.3              | 5.94/complies     |
|             | 30°C/60%RH          | 0.205          | 102.5   | 0.07                       | 0.07              | 2.00           | 100               | 0.281          | 100.4             | 5.99/complies     |
|             | 40°C/75%RH          | 0.203          | 101.5   | 0.07                       | 0.07              | 1.99           | 99.5              | 0.286          | 102.1             | 6.00/complies     |
| 4           | 30°C/60%RH          | 0.205          | 102.5   | 0.07                       | 0.07              | 1.97           | 98.5              | 0.280          | 100               | 5.99/complies     |
|             | 40°C/75%RH          | 0.203          | 101.5   | 0.08                       | 0.08              | 1.95           | 97.5              | 0.280          | 100               | 5.97/complies     |
|             | 50°C                | 0.204          | 102     | 0.06                       | 0.06              | 1.91           | 95.5              | 0.280          | 100               | 5.96/complies     |
|             |                     |                |         |                            |                   |                |                   |                |                   |                   |
| 13          | 25°C/60%RH          | 0.205          | 102.5   | 0.07                       | 0.15 <sup>c</sup> | 2.09           | 104.5             | 0.299          | 106.8             | 6.00/complies     |
|             | 30°C/60%RH          | 0.204          | 102.0   | 0.08                       | 0.15 <sup>c</sup> | 2.10           | 105               | 0.301          | 107.5             | 6.00/complies     |
|             | 40°C/75%RH          | 0.205          | 102.5   | 0.07                       | 0.07              | 1.89           | 94.5              | 0.279          | 99.6              | 6.03/complies     |
|             | 50°C                | 0.203          | 101.5   | 0.07                       | 0.14 <sup>d</sup> | 1.68           | 84.0              | 0.265          | 94.6              | 5.97/complies     |
| 26          | 5°C                 | 0.206          | 103     | <0.05                      | <0.05             | 1.99           | 99.5              | 0.284          | 101.4             | 5.94/complies     |
|             | 25°C/60%RH          | 0.206          | 103     | <0.05                      | <0.05             | 1.97           | 98.5              | 0.283          | 101.1             | 5.94/complies     |
|             | 30°C/60%RH          | 0.204          | 102     | <0.05                      | <0.05             | 1.94           | 97                | 0.280          | 100               | 5.99/complies     |
|             | 40°C/75%RH          | 0.202          | 101     | <0.05                      | <0.05             | 1.81           | 90.5              | 0.276          | 98.6              | 5.99/complies     |

<sup>a</sup> The solutions were stored in 4 oz (120 mL) glass bottles with child-resistant cap at 66-mL fill.  
The bottles were stored at an upright position except for photostability samples, where the bottles were stored lying on their side.  
<sup>b</sup> HIL/UVAB = Ultraviolet-A (range 320-400 nm) and high-intensity visible fluorescent light.  
The ICH guidelines of 200 watt hours/m<sup>2</sup> and 1.2 x10<sup>6</sup> lux hours are met after approximately 4 days.  
<sup>c</sup> The low preservative concentrations in the initial sample was due to assay problem. This was supported by the 98-100% results for the samples stored under the accelerated conditions.  
<sup>d</sup> An additional degradant with RRT of 1.8 (0.19% I.I.) was found in this sample.  
<sup>e</sup> An additional degradant with RRT of 2.33 was found at 0.07% and 0.08% I.I. level in the 25°C/60%RH and 30°C/60%RH samples, respectively.

*[Handwritten signature]*

Clearly, the data set forth above demonstrates that the liquid, ready-to-use entecavir compositions are extremely stable over an extended period of time at varying temperatures, even with the inclusion of a sweetener.

Liquid formulations containing from about 0.001 mg to about 10 mg of entecavir per mL are prepared according to the following procedures that ensure high potency and good uniformity of the product. The ready-to-use liquid compositions are prepared by first carefully dissolving preservatives and entecavir in water. The preservatives and entecavir are dissolved by stirring the solution with heating at a temperature about 40°C to about 80°C.

Once the preservatives and entecavir are dissolved, sweetener is added to the above solution. The solution is mixed with a mixer at a speed sufficient to form a vortex until the sweetener is dissolved.

After cooling the solution to below 35°C, one or more buffering agents and a flavoring agent are then added to the solution. The solution is mixed with any suitable mixer until both the buffering agent and the flavoring agent are dissolved. If necessary, the pH of the solution may be adjusted to about 5 to about 7 with a diluted acid or base. After adjusting the pH, the remaining water is added to make up the final volume of the batch. The final solution is mixed until uniform. The solution is bottled and stored at room temperature.

In a second embodiment of the present invention, the liquid entecavir composition is formulated from a powder for constitution as a liquid composition at the time of use. With a powder for constitution, the powder is mixed with a predetermined amount of water to form the liquid entecavir composition. One advantage to using a powder is that the stability of the powder can be maintained throughout its shelf life. The concentration of each component of the powder compositions of the present invention is reflected as a weight percent (wt.%) based on the total weight of the powder composition.

The antiviral agent entecavir is present in the powder composition in an amount about 0.001% to about 20%. Preferably, the entecavir is present in the powder composition in an amount about 0.003% to about 10%, more preferably about 0.005% to about 5%, and most preferably about 0.005% to about 1%.

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To overcome the bitterness associated with entecavir, and to make the composition palatable at the time of use, a sweetener, as set forth above for the liquid entecavir compositions, may be added to the powder composition. The sweeteners include, for example, sucrose, glucose, acesulfame, dextrose, sorbitol, xylitol, mannitol, or any combinations thereof. The sweetener is present in the powder composition in an amount about 30% to about 98%, based on the total weight of the powder composition. Preferably, sweetener is present in the composition in amount about 60% to about 95%.

To further enhance the palatability of the powder entecavir composition of the present invention, a flavoring agent, such as those set forth above for the liquid compositions, may be added to the powder for constitution composition. The flavoring agents include, for example, cherry, guarana, orange, banana, strawberry, vanilla, chocolate, or any combinations thereof. The flavoring agent may be included in the powder composition in an amount about 0.001 wt.% to about 1 wt.%. Preferably, flavoring agent is present in an amount about 0.01 wt.% to about 0.50 wt.%.

The powder for constitution composition of the present invention may also include a preservative, such as those set forth above for the liquid compositions of the present invention. The preservatives may include, for example, methylparaben, propylparaben, sodium benzoate, potassium sorbate, or any combinations thereof. The preservative may be present in the powder composition in an amount about 0.01 wt.% to about 5 wt.%. Preferably, preservative is present in an amount about 0.50 wt.% to about 3 wt.%.

The inclusion of a buffering agent to maintain a composition pH of about 5 to about 7 is important both for the stability of the entecavir powder composition with the sweetener and the preservative stability. Suitable buffering agents, such as those set forth above for the liquid entecavir compositions may be used. These buffering agents include, for example, citric acid, sodium citrate, phosphate buffer, acetate buffer, or any mixtures thereof. The buffering agent is included in the powder for constitution composition in an amount sufficient to maintain a composition pH of about 5 to about 7. Preferably, the molar concentration of the buffering agent is about 5 mM to about 200 mM. The buffering agent is present in the powder composition in

an amount about 1 to about 20%. Preferably, it is present in an amount about 5% to about 15%.

Three preferred liquid entecavir compositions formulated from a powder for constitution of the present invention are set forth in Tables 5 through 7 below.

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**TABLE 5**

**Powder for Constitution Entecavir (0.2 mg/mL) Liquid Formulation**

| Ingredients                                                                                                                         | Gram/100 ml             | Function        |
|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-----------------|
| Entecavir                                                                                                                           | 0.02                    | Antiviral Agent |
| Xylitol                                                                                                                             | 35.0                    | Sweetener       |
| Sodium Benzoate                                                                                                                     | 0.4                     | Preservative    |
| Cherry or Guarana                                                                                                                   | 0.05/0.025              | Flavoring Agent |
| Potassium Phosphate, monobasic (KH <sub>2</sub> PO <sub>4</sub> ) and Sodium Phosphate, dibasic (Na <sub>2</sub> HPO <sub>4</sub> ) | 2.58/0.04               | Buffering Agent |
| Purified Water                                                                                                                      | q.s. to 100 mL (pH 5.0) | Solvent         |

**TABLE 6**

**Powder for Constitution Entecavir (0.05 mg/mL) Liquid Formulation**

| Ingredients                                                                                                                         | Gram/100 ml             | Function        |
|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-----------------|
| Entecavir                                                                                                                           | 0.005                   | Antiviral Agent |
| Xylitol                                                                                                                             | 35.0                    | Sweetener       |
| Sodium Benzoate                                                                                                                     | 0.4                     | Preservative    |
| Cherry or Guarana                                                                                                                   | 0.05/0.025              | Flavoring Agent |
| Potassium Phosphate, monobasic (KH <sub>2</sub> PO <sub>4</sub> ) and Sodium Phosphate, dibasic (Na <sub>2</sub> HPO <sub>4</sub> ) | 2.58/0.04               | Buffering Agent |
| Purified Water                                                                                                                      | q.s. to 100 mL (pH 5.0) | Solvent         |

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TABLE 7

Powder for Constitution Entecavir (0.2 mg/mL) Liquid Formulation

| Ingredients                                                                                                                         | Gram/100 ml             | Function        |
|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-----------------|
| Entecavir                                                                                                                           | 0.02                    | Antiviral Agent |
| Mannitol                                                                                                                            | 15.0                    | Sweetener       |
| Sodium Benzoate                                                                                                                     | 0.4                     | Preservative    |
| Cherry or Guarana                                                                                                                   | 0.05/0.025              | Flavoring Agent |
| Potassium Phosphate, monobasic (KH <sub>2</sub> PO <sub>4</sub> ) and Sodium Phosphate, dibasic (Na <sub>2</sub> HPO <sub>4</sub> ) | 2.58/0.04               | Buffering Agent |
| Purified Water                                                                                                                      | q.s. to 100 mL (pH 5.0) | Solvent         |

5      The stability of the liquid entecavir compositions formulated from powders for constitution is demonstrated below in Tables 8 and 9.

TABLE 8

Stability of Powder for Constitution Entecavir (0.2 mg/mL) Liquid Formulation given in Table 5

| Time    | Storage Condition | In 100 mM Citric Buffer |              |                     |
|---------|-------------------|-------------------------|--------------|---------------------|
|         |                   | % of initial potency    |              | pH for both flavors |
|         |                   | With Cherry             | With Guarana |                     |
| 3 weeks | 5° C              | ND                      | 103          | 5.0                 |
|         | 40° C             | ND                      | 101.5        | 5.0                 |
|         | 50° C             | ND                      | 103          | 5.0                 |

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ND - Not determined

**TABLE 9**

**Stability of Powder for Constitution Entecavir (0.05 mg/mL) Liquid Formulation  
given in Table 6**

| Time    | Storage<br>Condition | In 100 mM Citric Buffer |              |                     |
|---------|----------------------|-------------------------|--------------|---------------------|
|         |                      | % of initial potency    |              | pH for both flavors |
|         |                      | With Cherry             | With Guarana |                     |
| 6 weeks | 5° C                 | 100                     | 100          | 5.0                 |
|         | 30° C                | 100                     | 100          | 5.0                 |
|         | 40° C                | 104                     | 98           | 5.0                 |
|         | 50° C                | 91                      | 80           | 5.0                 |

5           Clearly, the data set forth above demonstrates that the liquid entecavir compositions formed from a powder for constitution composition are extremely stable over an extended period of time at varying temperatures, even with the inclusion of sweetener.

10           The powder for constitution, entecavir liquid compositions of the present invention may be made by first formulating a powder composition. The powder composition is formed by mixing the entecavir, sweetener, preservative, flavoring agent, and buffering agent in a mixer or blender at a slow speed using geometric mixing. The resulting blend is subdivided in a wide mouth 100-mL bottle. Each bottle will have about 38 grams of blend. To form a liquid composition, the blend is  
15           constituted with an amount of water suitable to obtain the desired solution concentration of entecavir.

            It should be understood that while the above procedures are described for preparing pharmaceutical compositions containing from about 0.05 mg to about 0.2 mg of entecavir, they can also be employed to prepare pharmaceutical compositions  
20           containing low doses of any soluble pharmaceutically active substance.

            In another embodiment of the present invention, a hepatitis B virus infection may be treated with low dose entecavir liquid compositions as described above in combination with one or more additional pharmaceutically active agents.

            Suitable additional pharmaceutically active agents for this purpose include one  
25           or more antiviral agents, for example, didanosine, lamivudine, abacavir, adefovir,

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adefovir dipivoxil, famciclovir, (2R,4R)-4-(2,6-diamino-9H-purin-9-yl)-2-hydroxymethyl-1,3-dioxolane (DAPD), hepatitis B immunomodulating proteins (EHT 899 from Enzo Biochem), emtricitabine, 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine(FMAU), GLQ-223 (Compound A, alpha-trichosanthin),  
5 epavudine (L-dT), epcitabine (L-dC), ribavirin, tenofovir (PMPA), 2',3'-dideoxy-2',3'-didehydro-beta-L(-)-5-fluorocytidine[L(-)Fd4C], as well as other fluoro L- and D-nucleosides.

Suitable pharmaceutically active agents for this purpose may also include one or more immunomodulators, for example, alpha interferon, beta interferon, pegylated  
10 interferon, thymosin alpha, and hepatitis B vaccines such as HBV/MF59, Hepagene and Theradigm-HBV.

In another embodiment of the present invention, co-infected patients may be treated with the low dose liquid entecavir compositions described above. A co-infected patient is one infected with other viral or non-viral diseases in addition to  
15 hepatitis B. In particular, such treatment is possible for hepatitis B patients co-infected with hepatitis C or HIV. Such co-infected patients are preferably treated with the low dose liquid entecavir compositions as described above in combination with one or more other pharmaceutically active agents as described above. For example, a patient co-infected with hepatitis B and hepatitis C can be treated with the low dose  
20 liquid entecavir composition in addition to being treated with a regimen of ribavirin and an interferon.

The low dose liquid entecavir pharmaceutical compositions described above for daily administration may also be administered to certain patients less often. For example, patients who have been treated by daily administration of the low dose  
25 entecavir pharmaceutical compositions so that their hepatitis B virus infection is now under control may be placed on a maintenance regimen to protect against further infection. Such maintenance therapy may involve the administration of the low dose liquid entecavir composition on a less than daily basis. For example, a single dose administered every three or four days or administered on a weekly basis may be  
30 sufficient.

Surprisingly, it has been found that once daily administration of the low dose liquid entecavir pharmaceutical compositions of this invention are effective in treating

hepatitis B virus infection without undesirable side effects that can result from administration of the high dose regimen described in U.S. Patent No. 5,206,244.

The present invention having been thus been described with particular reference to the preferred forms thereof, it will be obvious that various changes and . 5 . modifications may be made therein without departing from the spirit and scope of the present invention as defined in the appended claims.

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/**WHAT IS CLAIMED IS:**

1. A liquid pharmaceutical composition to treat hepatitis B virus infection comprising a pharmaceutically acceptable solvent and about 0.001% to about 20% w/v of entecavir.
- 5 2. The liquid pharmaceutical composition of claim 1, wherein said entecavir is present in the composition in an amount of about 0.003% to about 10% w/v.
3. The liquid pharmaceutical composition of claim 2, wherein said entecavir is present in the composition in an amount of about 0.005% to about 5% w/v.
- 10 4. The liquid pharmaceutical composition of claim 3, wherein said entecavir is present in the composition in an amount of about 0.005% to about 1% w/v.
5. The liquid pharmaceutical composition of claim 1, further comprising at least one component selected from the group consisting of sweetener, preservative, 15 flavoring agent, buffering agent, pH adjusting agent, pharmaceutically active agent other than entecavir, and any combinations thereof.
6. The liquid pharmaceutical composition of claim 5, wherein said sweetener is selected from the group consisting of maltitol, sucrose, sorbitol, xylitol, 20 mannitol, and any combinations thereof and is present in an amount about 10% to about 85% w/v.
7. The liquid pharmaceutical composition of claim 5, wherein said preservative is selected from the group consisting of methylparaben, propylparaben, sodium benzoate, potassium sorbate, and any combinations thereof and is present in 25 an amount about 0.01% to about 1.0% w/v.
8. The liquid pharmaceutical composition of claim 5, wherein said flavoring agent is present in an amount about 0.001% to about 2% w/v.
9. The liquid pharmaceutical composition of claim 5, wherein said buffering agent is selected from the group consisting of citric acid, sodium citrate, 30 phosphate buffer, acetate buffer, and any combinations thereof and is present in an amount about 0.01% to about 5% w/v.

10. The liquid pharmaceutical composition of claim 5, wherein said pH adjusting agent is selected from the group consisting of dilute acid, dilute base, and any combinations thereof and is present in an amount to adjust said composition pH between about 5 and about 7.

5           11. The liquid pharmaceutical composition of claim 5, wherein said pharmaceutically active agent other than entecavir is selected from the group consisting of didanosine, lamivudine, abacavir, adefovir, adefovir dipivoxil, famciclovir, (2R,4R)-4-(2,6-diamino-9H-purin-9-yl)-2-hydroxymethyl-1,3-dioxolane (DAPD), hepatitis B immunomodulating proteins (EHT 899 from Enzo Biochem),  
10       emtricitabine, 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine(FMAU), GLQ-223 (Compound A, alpha-trichosanthin), epavudine (L-dT), epcitabine (L-dC), ribavirin, tenofovir (PMPA), 2',3'-dideoxy-2',3'-didehydro-beta-L(-)-5-fluorocytidine[L(-)Fd4C], fluoro L- and D- nucleosides, immunomodulators, and any combinations thereof.

12. The liquid pharmaceutical composition of claim 1, wherein said  
15       pharmaceutically acceptable solvent is selected from the group consisting of water, PEG 400, propylene glycol, ethanol, glycerin, and any combinations thereof.

13. The liquid pharmaceutical composition of claim 1, wherein said pharmaceutically acceptable solvent is water.

14. A powder for constitution at the time of use as a liquid pharmaceutical  
20       composition to treat hepatitis B virus infection comprising about 0.001 wt.% to about 20 wt.% of entecavir, based on the total weight of the powder composition.

15. The powder composition of claim 14, wherein said entecavir is present in the powder composition in an amount of about 0.003 wt.% to about 10 wt.% based on the total weight of the powder composition.

25       16. The powder composition of claim 15, wherein said entecavir is present in the powder composition in an amount of about 0.005 wt.% to about 5 wt.% based on the total weight of the powder composition.

17. The powder composition of claim 16, wherein said entecavir is present in the powder composition in an amount of about 0.005 wt.% to about 1 wt.% based on  
30       the total weight of the powder composition.

18. The powder composition of claim 14, further comprising at least one component selected from the group consisting of sweetener, preservative, flavoring

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agent, buffering agent, pH adjusting agent, pharmaceutically active agent other than entecavir, and any combinations thereof.

19. The powder composition of claim 18, wherein said sweetener is selected from the group consisting of sucrose, glucose, acesulfame, dextrose, sorbitol, xylitol, mannitol, and any combinations thereof and is present in an amount about 30 wt.% to about 98 wt.%.

20. The powder composition of claim 18, wherein said preservative is selected from the group consisting of methylparaben, propylparaben, sodium benzoate, potassium sorbate, and any combinations thereof and is present in an amount about 0.01 wt.% to about 5 wt.%.

21. The powder composition of claim 18, wherein said flavoring agent is present in an amount about 0.001 wt.% to about 1 wt.%.

22. The powder composition of claim 18, wherein said buffering agent is selected from the group consisting of citric acid, sodium citrate, phosphate buffer, acetate buffer, and any combinations thereof and is present in an amount about 1 wt.% to about 20 wt.%.

23. The powder composition of claim 18, wherein said pharmaceutically active agent other than entecavir is selected from the group consisting of didanosine, lamivudine, abacavir, adefovir, adefovir dipivoxil, famciclovir, (2R,4R)-4-(2,6-diamino-9H-purin-9-yl)-2-hydroxymethyl-1,3-dioxolane (DAPD), hepatitis B immunomodulating proteins (EHT 899 from Enzo Biochem), emtricitabine, 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine(FMAU), GLQ-223 (Compound A, alpha-trichosanthin), epavudine (L-dT), epcitabine (L-dC), ribavirin, tenofovir (PMPA), 2',3'-dideoxy-2',3'-didehydro-beta-L(-)-5-fluorocytidine[L(-)Fd4C], fluoro L- and D- nucleosides, immunomodulators, and any combinations thereof.

24. A method of preparing a liquid pharmaceutical composition for oral administration containing a low dose of entecavir comprising the step of dissolving said entecavir and preservative in a solution comprising a pharmaceutically acceptable solvent, wherein said entecavir is present in said solution in an amount about 0.001% to about 20% on a weight/volume basis of the solution.

25. The method of claim 24, wherein said pharmaceutically acceptable solvent is water.

26. The method of claim 24, further comprising the steps of:
- (a) dissolving a sweetener in said solution;
  - (b) dissolving a buffering agent in said solution; and
  - (c) dissolving a flavoring agent in said solution.
- 5        27. A method of preparing a powder for reconstitution at the time of use as a liquid pharmaceutical composition for oral administration containing a low dose of entecavir comprising the step of mixing entecavir with at least one additional component selected from the group consisting of sweetener, preservative, flavoring agent, buffering agent, and any combinations thereof, wherein the powder for
- 10 constitution is formed and wherein said entecavir is present in said powder for constitution composition in an amount about 0.001 wt.% to about 20 wt.%.
28. A liquid pharmaceutical composition comprising:
- about 0.001% to about 20% entecavir;
  - about 10% to about 85% sweetener;
  - 15 about 0.001% to about 0.1% flavoring agent;
  - about 0.01% to about 1% preservative;
  - about 0.01% to about 5% buffering agent; and
  - q.s. of pharmaceutically acceptable solvent,
  - wherein the percentages are on a weight/volume basis.
- 20        29. The liquid pharmaceutical composition of claim 28, wherein said entecavir is present in an amount about 0.003% to about 10% w/v.
30. The liquid pharmaceutical composition of claim 29, wherein said entecavir is present in an amount about 0.005% to about 5% w/v.
31. The liquid pharmaceutical composition of claim 30, wherein said
- 25 entecavir is present in an amount about 0.005% to about 1% w/v.
32. The liquid pharmaceutical composition of claim 28, wherein said entecavir is present in an amount about 0.005% w/v.
33. The liquid pharmaceutical composition of claim 28, wherein said entecavir is present in an amount about 0.02% w/v.
- 30        34. A powder for constitution at the time of use as a liquid pharmaceutical composition comprising:
- about 0.001 wt.% to about 20 wt.% entecavir;

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about 70 wt.% to about 90 wt.% sweetener;  
about 0.001 wt.% to about 1 wt.% flavoring agent;  
about 0.01 wt.% to about 5 wt.% preservative; and  
about 1 wt.% to about 20 wt.% buffering agent,

5        wherein the percentages are based on the total weight of said powder composition.

35. The powder composition of claim 34, wherein said entecavir is present in an amount about 0.003 wt.% to about 10 wt.% based on the total weight of said powder composition.

10        36. The powder composition of claim 35, wherein said entecavir is present in an amount about 0.005 wt.% to about 5 wt.% based on the total weight of said powder composition.

15        37. The powder composition of claim 36, wherein said entecavir is present in an amount about 0.005 wt.% to about 1 wt.% based on the total weight of said powder composition.

38. The powder composition of claim 34, wherein said entecavir is present in an amount about 0.013 wt.% based on the total weight of said powder composition.

39. The powder composition of claim 34, wherein said entecavir is present in an amount about 0.05 wt.% based on the total weight of said powder composition.

20        40. The powder composition of claim 34, wherein said entecavir is present in an amount about 0.11 wt.% based on the total weight of said powder composition.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/10371

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/36, 9/48  
US CL : 514/261; 424/451

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)

U.S. : 514/261; 424/451

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)  
WEST 2.1, STN, file REG, file MEDICINE, search terms: entecavir, low dose, oral, peroral, enteral, composition.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                          | Relevant to claim No. |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | US 2001/0033864 A1 (COLONNO et al.) 25 October 2001 (25.10.2001) see entire document.                                                                                       | 1-40                  |
| A          | MARION et al. Potent Efficacy of Entecavir (BMS90200475) in a Duck Model of Hepatitis B Virus Replication, Antimicrobial Agents and Chemotherapy, January 2002 pages 82-88. | 1-40                  |

☐ 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
- "B" earlier application or patent published on or after the international filing date
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Date of the actual completion of the international search

02 June 2003 (02.06.2003)

Date of mailing of the international search report

13 AUG 2003

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| (19) Organización Mundial de la Propiedad Intelectual<br>Oficina Internacional                                                                                                                  |                                    | A1                                                                                                                                                                                                                                                                                                                                                                                                              | (10) Número de Solicitud Internacional:<br>WO 02/086367 |
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| (71) Solicitante (para todos los estados designados excepto US): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Route 206 and Provincetown Road, Princeton, NJ 08543-4000 (US).           |                                    |                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                         |
| (72) Inventores: a                                                                                                                                                                              |                                    |                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                         |
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**(54) Título: FORMULACIONES LÍQUIDAS DE BAJA DOSIS DE ENTECAVIR Y USO**

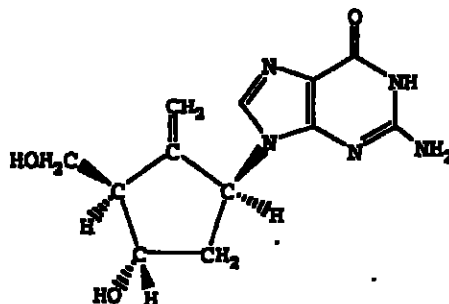
**(57) Resumen:** La presente invención proporciona composiciones farmacéuticas líquidas, que tienen una baja dosis de entecavir. En una modalidad de la presente invención, la composición líquida de entecavir es una composición lista para usar que está formulada para ser estable y de sabor agradable. En una segunda modalidad de la presente invención, la composición líquida de entecavir se formula de una composición en polvo en el momento de uso. Las composiciones de baja dosis de entecavir también pueden incluir por lo menos un componente seleccionado de edulcorante, conservador, agente saborizante, agente amortiguador, o combinaciones de estos. Las composiciones líquidas de entecavir también pueden formularse en combinación con otros agentes farmacéuticamente activos.

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## FORMULACIONES LIQUIDAS DE BAJA DOSIS DE ENTECAVIR Y USO

### ANTECEDENTES DE LA INVENCIÓN

El entecavir, [1S-(1 $\alpha$ ,3 $\alpha$ ,4 $\beta$ )]-2-amino-1,9-dihidro-9-[4-hidroxi-3-(hidroximetil)-2-metilenciclopentil]-6H-purin-6-ona, que tiene la estructura química



es un agente antiviral actualmente sometido a evaluación clínica para el tratamiento de la infección por el virus de la hepatitis B (VHB).

La patente U.S. No. 5,206,244 de Zahler et al., describe el entecavir y su uso en el tratamiento de la hepatitis B. Zahler describe que una dosis antiviral efectiva para administración oral o parenteral estará probablemente en el intervalo de aproximadamente 1.0 a 50 mg/kg de peso corporal y que la dosis deseada puede ser administrada varias veces por día a intervalos apropiados.

Se describen métodos mejorados para la síntesis de entecavir por Bisacchi et al, en WO 98/09964.

Las dosis bajas de formulaciones de entecavir, particularmente tabletas y cápsulas, se describen en la

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solicitud U.S. US-2001-0033864-A1 publicada el 25 de octubre de 2001 y la solicitud del PCT WO 01/64221 A1 publicada el 7 de septiembre de 2001.

BREVE DESCRIPCIÓN DE LA INVENCION

Es un objetivo de la presente invención proveer una composición farmacéutica líquida que tiene una dosis baja de entecavir capaz de tratar segura y efectivamente la infección por el virus de la hepatitis B.

Es otro objetivo de la presente invención proveer la composición de entecavir líquida de baja dosis que esté lista para usar.

Es todavía otro objetivo de la presente invención proveer tal composición de entecavir líquida de baja dosis que es tanto estable como de sabor agradable.

Es aún otro objetivo de la presente invención proveer así tal composición de entecavir líquida de baja dosis que está formulada a partir de un polvo para constitución como una composición líquida en el momento del uso.

Es un objetivo adicional de la presente invención proveer un proceso para formular una dosis baja, lista para usar, de una composición líquida de entecavir.

Es todavía un objetivo adicional de la presente invención proveer un proceso para formular una composición líquida de entecavir de dosis baja, de un polvo para constitución como una composición líquida en el momento del uso.

Estos y otros objetivos y ventajas de la presente invención se logran por una composición líquida farmacéutica que tiene una baja dosis de entecavir. En una modalidad de la presente invención, la composición líquida de entecavir es una composición lista para usar que se formula para ser tanto estable como de sabor agradable. En una segunda modalidad de la presente invención, la composición líquida de entecavir se formula de un polvo para constitución como una composición líquida en el momento del uso. Las composiciones de baja dosis de entecavir también tienen por lo menos un componente adicional seleccionado de uno o más de los siguientes: edulcorante, conservador, agente saborizante, agente de solución amortiguadora, agente de ajuste de pH, o cualesquiera combinaciones de estos. Las composiciones líquidas de entecavir también pueden ser formuladas en combinación con otros agentes farmacéuticamente activos.

#### DESCRIPCIÓN DETALLADA DE LA INVENCION

El entecavir es un potente agente antiviral, el cual ha demostrado buena eficacia contra el VHB. Puesto que el entecavir es muy potente, muy bajas dosis son suficientes para lograr los efectos terapéuticos deseados. Sin embargo, formulaciones de baja dosis, y particularmente formulaciones líquidas, plantean grandes retos a los formuladores porque el fármaco se degrada más rápido en estado líquido que en estado sólido. Cualquier degradación menor se traduce en una

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reducción significativa en la potencia.

Aunque el entecavir es potente, es también extremadamente amargo. Para combatir la amargura, se usa generalmente un edulcorante. Sin embargo, el entecavir ha demostrado tendencia a reaccionar con los edulcorantes usados comúnmente, tal como sacarosa, creando preocupaciones de estabilidad. El entecavir tiene un grupo de amina primaria en su estructura que tiene la propensión a reaccionar con cualquier edulcorante o agente saborizante que contenga grupos aldehídos y/o cetonas. Esta reacción es más pronunciada a un pH de ácido débil (pH 3 a 4), pero se minimiza a un pH de 5 a 7.

Esta invención se refiere a composiciones farmacéuticas líquidas que contienen una dosis baja del agente activo antiviral entecavir para una administración diaria, para tratar la infección por el virus de la hepatitis B en un paciente adulto humano o en un paciente pediátrico. Las composiciones líquidas farmacéuticas también tienen por lo menos un componente adicional seleccionado de uno o más de los siguientes: edulcorante, conservador, agente saborizante, agente de solución amortiguadora, agente de ajuste de pH, otros agentes farmacéuticamente activos, particularmente otros agentes antivirales o cualquier combinación de éstos.

El término paciente adulto humano se define como un paciente de alrededor de 16 años de edad o más y un peso

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igual a o mayor de aproximadamente 50 kilogramos. Las composiciones farmacéuticas que contienen entecavir en el límite inferior de los intervalos de arriba son apropiadas para administración a pacientes pediátricos o pacientes adultos que pesan menos que aproximadamente 50 kilogramos.

En una modalidad de la presente invención, la composición líquida de entecavir es una composición farmacéutica lista para usar. La concentración de cada componente presente en la composición líquida de entecavir se refleja en un por ciento en peso por volumen (% p/v). El agente antiviral entecavir está presente en la composición farmacéutica lista para usar, líquida, en una cantidad de alrededor de 0.001% a alrededor de 20%. De preferencia, el entecavir está presente en la composición en una cantidad de aproximadamente 0.003% a aproximadamente 10%, más preferentemente entre alrededor de 0.005% y alrededor de 5%, y más preferentemente entre alrededor de 0.005% y alrededor de 1%.

Para contrarrestar la amargura asociada con el entecavir y hacer de sabor agradable la composición, puede adicionarse un edulcorante a la composición. Los edulcorantes apropiados incluyen, por ejemplo, maltitol (Lycasin®), sacarosa, sorbitol xilitol, manitol o cualesquiera combinaciones de estos. El edulcorante está presente en la composición en una cantidad de aproximadamente 10% a aproximadamente 85%. De preferencia, el edulcorante está presente en una cantidad de

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aproximadamente 15% a aproximadamente 70%.

Para mejorar adicionalmente el sabor agradable de la composición de entecavir de la presente invención, puede ser adicionado un agente saborizante a la composición. Los agentes saborizantes apropiados incluyen, por ejemplo, cereza, guaraná, naranja, plátano, fresa, vainilla, chocolate o cualquier combinación de estos. El agente saborizante puede estar presente en la composición en una cantidad de aproximadamente 0.001% a aproximadamente 2%. De preferencia, el agente saborizante está presente en una cantidad de aproximadamente 0.01% a aproximadamente 0.075%.

La composición de la presente invención también puede incluir un conservador. Los conservadores apropiados incluyen, por ejemplo, metilparabeno, propilparabeno, butilparabeno, benzoato de sodio, sorbato de potasio, o cualquier combinación de estos. El conservador puede estar presente en la composición en una cantidad de aproximadamente 0.01% a aproximadamente 1.0%. De preferencia, el conservador está presente en una cantidad de aproximadamente 0.1% a aproximadamente 0.75%.

El pH de la composición puede ajustarse con cualquier ácido o base diluido apropiado. Por ejemplo, un ácido diluido apropiado es el ácido clorhídrico y una base diluida apropiada es el hidróxido de sodio. El pH de la composición es de preferencia de aproximadamente 5 a aproximadamente 7.

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X  
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La inclusión de un agente de solución amortiguadora para mantener un pH de la composición de aproximadamente 5 a aproximadamente 7 es importante tanto para la estabilidad del entecavir con el edulcorante como para la estabilidad del conservador. Agentes de solución amortiguadora apropiados incluyen, por ejemplo, ácido cítrico, citrato de sodio, solución amortiguadora de fosfato, solución amortiguadora de acetato, o cualesquiera combinaciones de estos. El agente de la solución amortiguadora está presente en la composición en una cantidad suficiente para mantener un pH de la composición de aproximadamente 5 a aproximadamente 7. De preferencia, la concentración molar del agente de solución amortiguadora está entre alrededor de 5 mM a alrededor de 200 mM. El agente de solución amortiguadora está presente en la composición en una cantidad de aproximadamente 0.01% a aproximadamente 5%.

Los componentes anteriores de la composición líquida de entecavir pueden formularse en solución con cualquier solvente apropiado farmacéuticamente aceptable. Un solvente apropiado farmacéuticamente aceptable incluye, por ejemplo, agua, PEG 400, propilen glicol, etanol, glicerina, o cualquier combinación de estos. De preferencia, el solvente farmacéuticamente aceptable es agua.

Dos composiciones líquidas de entecavir preferidas, listas para usar, de la presente invención se establecen en las Tablas 1 y 2 posteriores.

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**TABLA 1**

Formulación Líquida de Entecavir Lista para usar (RTU, por sus siglas en inglés) (0.2 mg/mL)

| Ingredientes                    | Gramo/100 ml                             | Función             |
|---------------------------------|------------------------------------------|---------------------|
| Entecavir                       | 0.02                                     | Agente Antiviral    |
| Maltitol (Lycasin®)             | 65.0                                     | Edulcorante         |
| Metilparabeno                   | 0.2                                      | Conservador         |
| Propilparabeno                  | 0.028                                    | Conservador         |
| Cereza o Guaraná o Naranja      | 0.05/0.025/0.025                         | Agente Saborizante  |
| Ácido Cítrico/ Citrato de Sodio | 0.96/1.47 (100mM) ó<br>0.037/0.24 (10mM) | Agente Amortiguador |
| Agua                            | c.s. a 100 mL<br>(pH 6.0)                | Solvente            |

**TABLA 2**

Formulación Líquida de Entecavir Lista para usar (RTU) (0.05 mg/mL)

| Ingredientes                    | Gramos/100 ml                            | Función              |
|---------------------------------|------------------------------------------|----------------------|
| Entecavir                       | 0.005                                    | Agente Antiviral     |
| Maltitol (Lycasin®)             | 65.0                                     | Edulcorante          |
| Metilparabeno                   | 0.2                                      | Conservador          |
| Propilparabeno                  | 0.028                                    | Conservador          |
| Cereza o Guaraná o Naranja      | 0.05/0.025/0.025                         | Agente Saborizante   |
| Ácido Cítrico/ Citrato de Sodio | 0.96/1.47 (100mM) ó<br>0.037/0.24 (10mM) | Agente Amortiguador. |
| Agua                            | c.s. a 100 mL<br>(pH 6.0)                | Solvente             |

La estabilidad de la composición líquida de entecavir lista para usar de la presente invención se demuestra abajo en las Tablas 3 y 4.

TABLA 3

Estabilidad de Entecavir listo para usar (RTU) Formulaci3n L3quida<sup>a</sup>, 0.05 mg/mL, en Botellas de Vidrio Transparentes

| Tiempo, semanas | Condici3n de almacenamiento      | Entecavir       |            | Impureza /Degradante % I.I. |                   | Metilparabeno  |            | Propilparabeno  |            | pH/ apariencia |
|-----------------|----------------------------------|-----------------|------------|-----------------------------|-------------------|----------------|------------|-----------------|------------|----------------|
|                 |                                  | Potencia, mg/mL | % Etiqueta | RRT 0.24                    | Total             | Potencia mg/mL | % Etiqueta | Potencia, mg/mL | % Etiqueta |                |
| Inicial         |                                  | 0.0508          | 101.8      | 0.07                        | 0.07              | 1.94           | 97         | 0.273           | 97.5       | 5.99/cumple    |
| 4 d3as          | 25°C/HIL/UVA <sup>8</sup> ,PROT  | 0.0508          | 101.2      | 0.07                        | 0.07              | 1.98           | 99         | 0.277           | 98.9       | 6.02/cumple    |
|                 | 25°C/HIL/UVA <sup>8</sup> ,EXPOS | 0.0503          | 100.8      | 0.07                        | 0.07              | 1.98           | 99         | 0.278           | 99.3       | 6.03/cumple    |
| 2               | 25°C/HIL/UVA <sup>8</sup> ,PROT  | 0.0508          | 101.2      | 0.07                        | 0.07              | 2.00           | 100        | 0.284           | 101.4      | 5.67/cumple    |
|                 | 25°C/HIL/UVA <sup>8</sup> ,EXPOS | 0.0499          | 99.8       | 0.07                        | 0.74 <sup>e</sup> | 1.98           | 98.0       | 0.279           | 99.6       | 5.91/cumple    |
|                 | 30°C/60% de HR                   | 0.0512          | 102.4      | 0.08                        | 0.08              | 2.0            | 100        | 0.281           | 100.4      | 6.02/cumple    |
|                 | 40°C/75% de HR                   | 0.0513          | 102.8      | 0.09                        | 0.09              | 1.99           | 99.5       | 0.278           | 99.3       | 6.03/cumple    |
| 4               | 30°C/80% de HR                   | 0.0509          | 101.8      | 0.07                        | 0.07              | 1.97           | 98.5       | 0.280           | 100        | 6.03/cumple    |
|                 | 40°C/75% de HR                   | 0.0509          | 101.8      | 0.07                        | 0.07              | 1.95           | 97.5       | 0.279           | 99.8       | 6.01/cumple    |
|                 | 50°C                             | 0.0505          | 101.0      | 0.08                        | 0.08              | 1.89           | 94.5       | 0.276           | 98.6       | 6.00/cumple    |
| 13              | 25°C/80% de HR                   | 0.0509          | 101.8      | 0.07                        | 0.07              | 2.00           | 100        | 0.286           | 102.1      | 6.03/cumple    |
|                 | 30°C/80% de HR                   | 0.0515          | 103.0      | 0.07                        | 0.07              | 1.97           | 98.5       | 0.282           | 100.7      | 6.01/cumple    |

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|    |                | Entecavir |       | Impureza /Degradante % I.I. |       | Metilparabeno |      | Propilparabeno |       |             |
|----|----------------|-----------|-------|-----------------------------|-------|---------------|------|----------------|-------|-------------|
|    |                |           |       |                             |       |               |      |                |       |             |
| 26 | 40°C/75% de HR | 0.0508    | 101.6 | 0.07                        | 0.07  | 1.91          | 95.5 | 0.281          | 100.4 | 6.00/cumple |
|    | 50°C           | 0.0500    | 100.0 | 0.05                        | 0.05  | 1.73          | 86.5 | 0.272          | 97.1  | 5.99/cumple |
|    | 5°C            | 0.0512    | 102.4 | <0.05                       | <0.05 | 2.00          | 100  | 0.284          | 101.4 | 5.99/cumple |
|    | 25°C/60% de HR | 0.0509    | 101.8 | <0.05                       | <0.05 | 1.96          | 98   | 0.281          | 100.4 | 6.00/cumple |
|    | 30°C/60% de HR | 0.0510    | 102   | <0.05                       | <0.05 | 1.94          | 97   | 0.280          | 100.0 | 5.99/cumple |
|    | 40°C/75% de HR | 0.0501    | 100.2 | <0.05                       | <0.05 | 1.80          | 90   | 0.274          | 97.9  | 5.99/cumple |

- a Las soluciones se almacenaron en botellas de cristal de 4 oz (120 mL) con tapa a prueba de niños lleno a 66-mL.  
Las botellas se almacenaron en una posición vertical excepto para muestras de fotoestabilidad, donde las botellas se almacenaron recostadas.
- b HIL/UVA = Ultravioleta-A (intervalo 320-400 nm) y luz fluorescente visible de alta-intensidad.  
Las directrices ICH de 200 vatios horas/m<sup>2</sup> y 1.2 x 10<sup>6</sup> horas lux se establecen después de aproximadamente 4 días.
- c Dos degradantes adicionales con RRT de 1.8 (0.61 % I.I.) y 2.1 (0.05% I.I.) se detectaron en esta muestra.

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HR = humedad relativa  
RRT = tiempo de retención relativo  
PROT = protegido (botella con tapa)  
EXPOS = no protegido (sin tapa)

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TABLA 4

Estabilidad de Entecavir Listo para uso (RTU) Formulaci3n L3quida\*, 0.2 mg/mL, en  
Botellas de Vidrio Transparentes

| Tiempo,<br>semanas | Condici3n de<br>almacenamiento | Entecavir          |               | Impureza<br>/Degradante<br>% I.I. |       | Metilparabeno     |                   | Propilparabeno     |                   | pH/<br>aparencia |
|--------------------|--------------------------------|--------------------|---------------|-----------------------------------|-------|-------------------|-------------------|--------------------|-------------------|------------------|
|                    |                                | Potencia,<br>mg/mL | %<br>Etiqueta | RRT<br>0.24                       | Total | Potencia<br>mg/mL | %<br>Etiqueta     | Potencia,<br>mg/mL | %<br>Etiqueta     |                  |
| Inicial            |                                | 0.204              | 102           | 0.07                              | 0.07  | 1.87              | 93.5 <sup>c</sup> | 0.264              | 94.3 <sup>c</sup> | 5.98/cumple      |
| 4 d3as             | 25°C/HIL/UVa*,PROT             | 0.201              | 100.5         | 0.07                              | 0.07  | 1.96              | 98                | 0.277              | 98.9              | 6.02/cumple      |
|                    | 25°C/HIL/UVa*,EXPOS            | 0.200              | 100           | 0.06                              | 0.06  | 1.95              | 97.5              | 0.275              | 98.2              | 6.04/cumple      |
| 2                  | 25°C/HIL/UVa*,PROT             | 0.203              | 101.5         | 0.07                              | 0.07  | 1.99              | 99.5              | 0.282              | 100.7             | 5.75/cumple      |

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|    |                                  | Entecavir |       | Impureza<br>/Degradante<br>% I.I. |                   | Metilparabeno |       | Propilparabeno |       |             |
|----|----------------------------------|-----------|-------|-----------------------------------|-------------------|---------------|-------|----------------|-------|-------------|
|    |                                  |           |       |                                   |                   |               |       |                |       |             |
|    | 25°C/HILUVA <sup>®</sup> , EXPOS | 0.199     | 99.5  | 0.07                              | 0.26 <sup>b</sup> | 1.97          | 98.5  | 0.278          | 99.3  | 5.94/cumple |
|    | 30°C/60% de HR                   | 0.205     | 102.5 | 0.07                              | 0.07              | 2.00          | 100   | 0.281          | 100.4 | 5.99/cumple |
|    | 40°C/75% de HR                   | 0.203     | 101.5 | 0.07                              | 0.07              | 1.99          | 99.5  | 0.286          | 102.1 | 6.00/cumple |
| 4  | 30°C/60% de HR                   | 0.205     | 102.5 | 0.07                              | 0.07              | 1.97          | 98.5  | 0.280          | 100   | 5.99/cumple |
|    | 40°C/75% de HR                   | 0.203     | 101.5 | 0.08                              | 0.08              | 1.95          | 97.5  | 0.280          | 100   | 5.97/cumple |
|    | 50°C                             | 0.204     | 102   | 0.06                              | 0.06              | 1.91          | 95.5  | 0.280          | 100   | 5.98/cumple |
| 13 | 25°C/60% de HR                   | 0.205     | 102.5 | 0.07                              | 0.15 <sup>a</sup> | 2.09          | 104.5 | 0.299          | 106.8 | 6.00/cumple |
|    | 30°C/60% de HR                   | 0.204     | 102.0 | 0.08                              | 0.15 <sup>a</sup> | 2.10          | 105   | 0.301          | 107.5 | 6.00/cumple |
|    | 40°C/75% de HR                   | 0.205     | 102.5 | 0.07                              | 0.07              | 1.89          | 94.5  | 0.279          | 99.6  | 6.03/cumple |
|    | 50°C                             | 0.203     | 101.5 | 0.07                              | 0.14 <sup>i</sup> | 1.68          | 84.0  | 0.285          | 94.6  | 5.97/cumple |
| 26 | 5°C                              | 0.206     | 103   | <0.05                             | <0.05             | 1.99          | 99.5  | 0.284          | 101.4 | 5.94/cumple |
|    | 25°C/60% de HR                   | 0.206     | 103   | <0.05                             | <0.05             | 1.97          | 98.5  | 0.283          | 101.1 | 5.94/cumple |
|    | 30°C/60% de HR                   | 0.204     | 102   | <0.05                             | <0.05             | 1.94          | 97    | 0.280          | 100   | 5.99/cumple |
|    | 40°C/75% de HR                   | 0.202     | 101   | <0.05                             | <0.05             | 1.81          | 90.5  | 0.276          | 98.6  | 5.99/cumple |

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- a Las soluciones se almacenaron en botellas de cristal de 4 oz (120 mL) con tapa a prueba de niños lleno a 66-mL.  
Las botellas se almacenaron en una posición vertical excepto para muestras de fotoestabilidad, donde las botellas fueron almacenadas recostadas.
- b HIL/UVA = Ultravioleta-A (intervalo 320-400 nm) y luz fluorescente visible de alta-intensidad.  
Las directrices ICH de 200 vatios horas/m<sup>2</sup> y 1.2 x 10<sup>6</sup> horas lux se encuentran después de aproximadamente 4 días.
- c Las bajas concentraciones de conservador en la muestra inicial fueron debidas a problemas de ensayo. Estas estuvieron soportadas por el 98-100% de los resultados para las muestras almacenadas bajo las condiciones aceleradas.
- d Un degradante adicional con RRT de 1.8 (0.19% I.I.) se encontró en estas muestras.
- e Un degradante adicional con RRT de 2.33 se encontró al nivel 0.07% y 0.08% I.I. en las muestras 25°C/60% de HR y 30°C/60% de HR, respectivamente.

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De manera clara, los datos mostrados arriba demuestran que las composiciones de entecavir, líquidas listas para usar son extremadamente estables durante un periodo prolongado de tiempo en temperaturas variables, aun con la inclusión de un edulcorante.

Las formulaciones líquidas que contienen de aproximadamente 0.001 mg a aproximadamente 10 mg de entecavir por mL se preparan de acuerdo con los siguientes procedimientos que aseguran alta potencia y uniformidad del producto. Las composiciones líquidas listas para usar se preparan primero disolviendo cuidadosamente los conservadores y el entecavir en agua. Los conservadores y el entecavir se disuelven por agitación de la solución con calentamiento a una temperatura de aproximadamente 40°C a aproximadamente 80°C.

Una vez que los conservadores y el entecavir se disuelven, el edulcorante se adiciona a la solución de anterior. La solución se mezcla con un mezclador a una velocidad suficiente para formar un vórtice hasta que se disuelve el edulcorante.

Después de enfriar la solución abajo de 35°C, uno o más agentes de solución amortiguadora y un agente saborizante se adicionan después a la solución. La solución se mezcla con cualquier mezclador apropiado hasta que se disuelven el agente de solución amortiguadora y el agente saborizante. Si es necesario, el pH de la solución puede ser ajustado de

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H

aproximadamente 5 a aproximadamente 7 con un ácido o base diluida. Después de ajustar el pH, el agua remanente se adiciona para cubrir el volumen final del lote. La solución final se mezcla hasta ser uniforme. La solución se embotella y almacena a temperatura ambiente.

En una segunda modalidad de la presente invención, la composición líquida de entecavir se formula de un polvo para constitución como una composición líquida en el momento del uso. Con un polvo para constitución, el polvo se mezcla con una cantidad predeterminada de agua para formar la composición líquida de entecavir. Una ventaja de usar un polvo es que la estabilidad del polvo puede mantenerse a través de su vida de anaquel. La concentración de cada componente de las composiciones en polvo de la presente invención está reflejada como un por ciento en peso (%p) basado en el peso total de la composición en polvo.

El agente antiviral entecavir está presente en la composición en polvo en una cantidad de aproximadamente 0.001% a alrededor de 20%. De preferencia, el entecavir está presente en la composición en polvo en una cantidad de aproximadamente 0.003% a aproximadamente 10%, más preferentemente aproximadamente 0.005% a aproximadamente 5%, y todavía más preferentemente aproximadamente 0.005% a aproximadamente 1%.

Para superar la amargura asociada con el entecavir, y hacer la composición de sabor agradable en el momento de uso,

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un edulcorante, como se mencionó arriba para las composiciones líquidas de entecavir, puede adicionarse a la composición en polvo. Los edulcorantes incluyen, por ejemplo, sacarosa, glucosa, acesulfame, dextrosa, sorbitol, xilitol, manitol, o cualquier combinación de estos. El edulcorante está presente en la composición en polvo en una cantidad de aproximadamente 30% a aproximadamente 98%, basado en el peso total de la composición en polvo. De preferencia, el edulcorante está presente en la composición en un cantidad de aproximadamente 60% a aproximadamente 95%.

Para mejorar adicionalmente el sabor de la composición en polvo de entecavir de la presente invención, un agente saborizante, tal como los mencionados para las composiciones líquida, puede adicionarse al polvo para la constitución de la composición. Los agentes saborizantes incluyen, por ejemplo, cereza, guaraná, naranja, plátano, fresa, vainilla, chocolate, o cualquier combinación de estos. El agente saborizante puede incluirse en la composición en polvo en una cantidad de aproximadamente 0.001% en peso a aproximadamente 1% en peso. De preferencia, el agente saborizante está presente en una cantidad de aproximadamente 0.01% en peso a aproximadamente 0.50% en peso.

El polvo para la composición de constitución de la presente invención también puede incluir un conservador, tal como los mencionados arriba para la composición líquida de la

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presente invención. Los conservadores pueden incluir, por ejemplo, metilparabeno, propilparabeno, benzoato de sodio, sorbato de potasio, y/o combinaciones de estos. Los conservadores pueden estar presentes en la composición en polvo en una cantidad de aproximadamente 0.01% en peso a aproximadamente 5% en peso. De preferencia, el conservador está presente en una cantidad de aproximadamente 0.50% en peso a aproximadamente 3% en peso. "

La inclusión de un agente amortiguador para mantener un pH de la composición de aproximadamente 5 a aproximadamente 7 es importante para la estabilidad de la composición en polvo del entecavir con el edulcorante y la estabilidad del conservador. Pueden usarse los agentes de solución amortiguadora apropiados, tales como los descritos arriba para las composiciones líquidas de entecavir. Los agentes de soluciones amortiguadoras incluyen, por ejemplo, ácido cítrico, citrato de sodio, solución amortiguadora fosfatada, solución amortiguadora de acetato, o cualquier combinación de estos. El agente amortiguador se incluye en el polvo para la composición de constitución en una cantidad suficiente para mantener un pH de la composición de aproximadamente 5 a aproximadamente 7. De preferencia, la concentración molar del agente amortiguador es de aproximadamente 5 mM a aproximadamente 200 mM. El agente amortiguador está presente en la composición en polvo en una cantidad de aproximadamente 1% a aproximadamente 20%. De

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preferencia, está presente en una cantidad de aproximadamente 5% a aproximadamente 15%.

Tres composiciones líquidas preferidas de entecavir formuladas de un polvo para constitución de la presente invención se representan en las Tablas 5 a 7 posteriores.

**TABLA 5**

Polvo para constitución de Entecavir (0.2 mg/mL)

Formulación Líquida.

| Ingredientes                                                                                                            | Gramos/100 ml             | Función             |
|-------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------|
| Entecavir                                                                                                               | 0.02                      | Agente antiviral    |
| Xilitol                                                                                                                 | 35.0                      | Edulcorante         |
| Benzoato de Sodio                                                                                                       | 0.4                       | Conservador         |
| Cereza o Guaraná                                                                                                        | 0.05/0.025                | Agente Saborizante  |
| Fosfato de Potasio, monobásico ( $\text{KH}_2\text{PO}_4$ ) y Fosfato de Potasio dibásico ( $\text{Na}_2\text{HPO}_4$ ) | 2.58/0.04                 | Agente Amortiguador |
| Agua Purificada                                                                                                         | c.s. a 100 mL<br>(pH 5.0) | Solvente            |

**TABLA 6**

Polvo para constitución de Entecavir (0.05 mg/mL)

Formulación Líquida.

| Ingredientes                                                                                                            | Gramos/100 ml             | Función              |
|-------------------------------------------------------------------------------------------------------------------------|---------------------------|----------------------|
| Entecavir                                                                                                               | 0.005                     | Agente Antiviral     |
| Xilitol                                                                                                                 | 35.0                      | Edulcorante          |
| Benzoato de Sodio                                                                                                       | 0.4                       | Conservador          |
| Cereza o Guaraná                                                                                                        | 0.05/0.025                | Agente Saborizante   |
| Fosfato de Potasio, monobásico ( $\text{KH}_2\text{PO}_4$ ) y Fosfato de Potasio dibásico ( $\text{Na}_2\text{HPO}_4$ ) | 2.58/0.04                 | Agente Amortiguador. |
| Agua Purificada                                                                                                         | c.s. a 100 mL<br>(pH 5.0) | Solvente             |

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TABLA 7

Polvo para constitución de Entecavir (0.2 mg/mL)  
Formulación Líquida.

| Ingredientes                                                                                                                        | Gramos/100 ml          | Función             |
|-------------------------------------------------------------------------------------------------------------------------------------|------------------------|---------------------|
| Entecavir                                                                                                                           | 0.02                   | Agente Antiviral    |
| Manitol                                                                                                                             | 15.0                   | Edulcorante         |
| Benzoato de Sodio                                                                                                                   | 0.4                    | Conservador         |
| Cereza o Guaraná                                                                                                                    | 0.05/0.025             | Agente Saborizante  |
| Fosfato de Potasio, monobásico (KH <sub>2</sub> PO <sub>4</sub> ) y Fosfato de Potasio dibásico (Na <sub>2</sub> HPO <sub>4</sub> ) | 2.58/0.04              | Agente Amortiguador |
| Agua Purificada                                                                                                                     | c.s. a 100 mL (pH 5.0) | Solvente            |

La estabilidad de las composiciones líquidas de entecavir formuladas a partir de polvos para constitución se demuestra a continuación en las Tablas 8 y 9.

TABLA 8

Estabilidad De Polvo para Constitución de Entecavir (0.2 mg/mL) Formulación Líquida dada en Tabla 5

| Tiempo    | Condición de almacenamiento | En Solución amortiguadora Cítrica 100 mM |             |                       |
|-----------|-----------------------------|------------------------------------------|-------------|-----------------------|
|           |                             | % de potencia inicial                    |             | PH para ambos sabores |
|           |                             | Con Cereza                               | Con Guaraná |                       |
| 3 semanas | 5° C                        | ND                                       | 103         | 5.0                   |
|           | 40° C                       | ND                                       | 101.5       | 5.0                   |
|           | 50° C                       | ND                                       | 103         | 5.0                   |

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ND - No determinado

TABLA 9

Estabilidad de Polvo para Constitución de Entecavir  
(0.05 mg/mL) Formulaci3n L3quida dada en Tabla 6

| Tiempo    | Condici3n de almacenamiento | En Soluci3n Amortiguadora C3trica 100 mM |             |                       |
|-----------|-----------------------------|------------------------------------------|-------------|-----------------------|
|           |                             | % de potencia inicial                    |             | PH para ambos sabores |
|           |                             | Con Cereza                               | Con Guaran3 |                       |
| 6 semanas | 5° C                        | 100                                      | 100         | 5.0                   |
|           | 30° C                       | 100                                      | 100         | 5.0                   |
| 6 semanas | 40° C                       | 104                                      | 98          | 5.0                   |
|           | 50° C                       | 91                                       | 80          | 5.0                   |

Claramente, los datos establecidos arriba demuestran que las composiciones l3quidas de entecavir formadas a partir de un polvo para constituci3n de la composici3n son extremadamente estables en un per3odo prolongado de tiempo a temperaturas variadas, aun con la inclusi3n del edulcorante.

El polvo para constituci3n, las composiciones l3quidas de entecavir de la presente invenci3n pueden elaborarse formulando primero una composici3n en polvo. La composici3n en polvo se forma mezclando el entecavir, edulcorante, conservador, agente saborizante, y agente amortiguador en un mezclador a una velocidad baja usando mezclado geom3trico. La mezcla resultante se subdivide en una botella de 100 mL de boca ancha. Cada botella tendr3 alrededor de 38 gramos de

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mezcla. Para formar una composición líquida, la mezcla está constituida con una cantidad de agua apropiada para obtener la concentración deseada de entecavir en la solución.

Deberá entenderse que mientras los procedimientos anteriores se describen para la preparación de composiciones farmacéuticas que contienen aproximadamente 0.05 mg a aproximadamente 0.2 mg de entecavir, también pueden emplearse para preparar composiciones farmacéuticas que contienen bajas dosis de cualquier sustancia farmacéuticamente activa soluble.

En otra modalidad de la presente invención, una infección por el virus de la hepatitis B puede ser tratada con composiciones líquidas de bajas dosis de entecavir como las descritas arriba en combinación con uno o más agentes farmacéuticamente activos adicionales.

Los agentes apropiados farmacéuticamente activos adicionales para este propósito incluye uno o más agentes antivirales, por ejemplo, didanosina, lamivudina, abacavir, adefovir, adefovir dipivoxil, famciclovir, (2R,4R)-4-(2,6-diamino-9H-purin-9-yl)-2-hidroximetil-1,3-dioxolano (DAPD), proteínas inmunomoduladoras de hepatitis B (EHT 899 de Enzo Biochem), emtricitabina, 1-(2-desoxi-2-fluoro-β-D-arabinofuranosil)timina (FMAU), GLQ-223 (Compuesto A, alfa-tricosantin), epavudina (L-dT), epcitabina (L-dC), ribavirin, tenofovir (PMPA), 2',3'-didesoxi-2',3'-dideshidro-beta-L(-)-

5-fluorocitidina[L(-)Fd4C], así como otro fluoro L- y D-nucleósidos.

Los agentes farmacéuticamente activos apropiados para este propósito también pueden incluir uno o más inmunomoduladores, por ejemplo, alfa interferón, beta interferón, interferón pegilado, timosin alfa, y vacunas de hepatitis B tales como HBV/MF59, Hepagene y Theradigm-HBV.

En otra modalidad de la presente invención, los pacientes co-infectados pueden ser tratados con las composiciones líquidas de baja dosis de entecavir descritas arriba. Un paciente co-infectado es uno infectado con otra enfermedad viral o no viral además de la hepatitis B. En particular, tal tratamiento es posible para pacientes de hepatitis B co-infectados con hepatitis C o VIH. Tales pacientes co-infectados se tratan preferentemente con composiciones líquidas de baja dosis de entecavir como las descritas arriba en combinación con uno o más de otros agentes farmacéuticamente activos como los descritos arriba. Por ejemplo, un paciente co-infectado con hepatitis B y hepatitis C puede ser tratado con la composición líquida de baja dosis de entecavir además de ser tratado con un régimen de ribavirin y un interferón.

Las composiciones farmacéuticas líquidas de baja dosis de entecavir descritas arriba para administración diaria, también pueden administrarse menos frecuentemente a ciertos

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pacientes. Por ejemplo, los pacientes que han sido tratados por administración diaria de composiciones farmacéuticas de baja dosis de entecavir, de manera que su infección con virus de hepatitis B está ahora bajo control, pueden ser puestos en un régimen de mantenimiento para protegerlos contra una infección posterior. Tal terapia de mantenimiento puede involucrar la administración de la composición líquida de baja dosis de entecavir en bases menores a las diarias. Por ejemplo, puede ser suficiente una única dosis administrada cada tres o cuatro días o administrada sobre una base semanal.

Sorpresivamente, se ha encontrado que la administración una vez al día de las composiciones líquidas farmacéuticamente activas de baja dosis de entecavir de esta invención son efectivas para tratar una infección de virus de hepatitis B sin efectos colaterales indeseables, que pueden resultar de la administración del régimen de dosis alta descrito en la Patente U.S. No. 5,206,244.

De esta manera, la presente invención habiéndose descrito con particular referencia a las formas preferidas, será obvio que pueden hacerse varios cambios y modificaciones en la misma sin apartarse del espíritu y alcance de la presente invención como se define en las reivindicaciones adjuntas.

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~~40~~REIVINDICACIONES

1. Una composición farmacéutica líquida para tratar infecciones por el virus de hepatitis B, caracterizada porque comprende un solvente farmacéuticamente aceptable y alrededor de 0.001% hasta alrededor de 20% p/v de entecavir.

2. La composición líquida farmacéutica de conformidad con la reivindicación 1, caracterizada porque el entecavir está presente en la composición en una cantidad de alrededor 0.003% a alrededor de 10% p/v.

3. La composición líquida farmacéutica de conformidad con la reivindicación 2, caracterizada porque el entecavir está presente en la composición en una cantidad de alrededor de 0.005% a alrededor de 5% p/v.

4. La composición líquida farmacéutica de conformidad con la reivindicación 3, caracterizada porque el entecavir está presente en la composición en una cantidad de alrededor de 0.005% a alrededor de 1% p/v.

5. La composición líquida farmacéutica de conformidad con la reivindicación 1, caracterizada porque además comprende por lo menos un componente seleccionado del grupo consiste de edulcorante, conservador, agente saborizante, agente de solución amortiguadora, agente para ajuste de pH, agente farmacéuticamente activo distinto a entecavir, y cualesquiera combinaciones de éstos.

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6. La composición líquida farmacéutica de conformidad con la reivindicación 5, caracterizada porque el edulcorante se selecciona del grupo que consiste de maltitol, sacarosa, sorbitol, xilitol, manitol, y cualesquiera combinaciones de éstos, y está presente en una cantidad alrededor de 10% a alrededor 85% p/v.

7. La composición líquida farmacéutica de conformidad con la reivindicación 5, caracterizada porque el conservador se selecciona del grupo que consiste de metilparabeno, propilparabeno, benzoato de sodio, sorbato de potasio, y cualesquiera de las combinaciones de éstos y está presente en una cantidad de alrededor de 0.01% a alrededor de 1.0% p/v.

8. La composición líquida farmacéutica de conformidad con la reivindicación 5, caracterizada porque el agente saborizante está presente en una cantidad de alrededor de 0.001% a alrededor de 2% p/v.

9. La composición líquida farmacéutica de conformidad con la reivindicación 5, caracterizada porque el agente de solución amortiguadora se selecciona del grupo que consiste de ácido cítrico, citrato de sodio, solución amortiguadora de fosfato, solución amortiguadora de acetato, y cualesquiera de las combinaciones de éstos y está presente en una cantidad de alrededor de 0.01% a alrededor de 5% p/v.

10. La composición líquida farmacéutica de conformidad con la reivindicación 5, caracterizada porque el agente de

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ajuste de pH se selecciona del grupo que consiste de ácido diluido, base diluida, y cualesquiera combinaciones de éstos y está presente en una cantidad para ajustar el pH de la composición entre alrededor de 5 y alrededor de 7.

11. La composición líquida farmacéutica de conformidad con la reivindicación 5, caracterizada porque el agente farmacéuticamente activo diferente al entecavir se selecciona del grupo que consiste de didanosina, lamivudina, abacavir, adefovir, adefovir dipivoxil, famciclovir, (2R, 4R)-4-(2,6-diamino-9H-purin-9-il)-2-hidroximetil-1,3-dioxolano (DAPD), proteínas inmunomoduladoras de hepatitis B (EHT 899 de Enzo Biochem), emtricitabina, 1-(2-desoxi-2-fluoro-β-D-arabinofuranosil)timina(FMAU), GLQ-223 (Compuesto A, alfa-tricosantin), epavudina (L-dT), epcitabina(L-dC), ribavirin, tenofovir (PMPA), 2',3'-didesoxi-2',3'-dideshidro-beta-L(-)-5-fluorocitidina[L(-)Fd4C], fluoro L- y D-nucleósidos, inmunomoduladores, y cualesquiera combinaciones de éstos.

12. La composición líquida farmacéutica de conformidad con la reivindicación 1, caracterizada porque el solvente farmacéuticamente aceptable se selecciona del grupo que consiste de agua, PEG 400, propilenglicol, etanol, glicerina, y cualesquiera combinaciones de éstos.

13. La composición líquida farmacéutica de conformidad con la reivindicación 1, caracterizada porque el solvente farmacéuticamente aceptable es agua.

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14. Un polvo para constitución en el momento de uso como una composición farmacéutica líquida para tratar la infección por el virus de hepatitis B, caracterizado porque comprende alrededor de 0.001 % en peso hasta alrededor de 20% en peso de entecavir, basado en el peso total de la composición en polvo.

15. La composición en polvo de conformidad con la reivindicación 14, caracterizada porque el entecavir está presente en la composición en polvo en una cantidad de alrededor de 0.003% en peso hasta alrededor de 10% en peso basado en el peso total de la composición en polvo.

16. La composición en polvo de conformidad con la reivindicación 15, caracterizada porque el entecavir está presente en la composición en polvo en una cantidad de alrededor de 0.005% en peso hasta alrededor de 5% en peso basado en el peso total de la composición en polvo.

17. La composición en polvo de conformidad con la reivindicación 16, caracterizada porque el entecavir está presente en la composición en polvo en una cantidad de alrededor de 0.005% en peso hasta alrededor de 1% en peso basado en el peso total de la composición en polvo.

18. La composición en polvo de conformidad con la reivindicación 14, caracterizada porque además comprende por lo menos un componente seleccionado del grupo que consiste de edulcorante, conservador, agente saborizante, agente de

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solución amortiguadora, agente de ajuste de pH, agente farmacéuticamente activo además del entecavir, y cualesquiera combinaciones de éstos.

19. La composición en polvo de conformidad con la reivindicación 18, caracterizada porque el edulcorante se selecciona del grupo que consiste de sacarosa, glucosa, acesulfame, dextrosa, sorbitol, xilitol, manitol, y cualesquiera combinaciones de éstos y está presente en una cantidad alrededor de 30% en peso hasta alrededor de 98% en peso.

20. La composición en polvo de conformidad con la reivindicación 18, caracterizada porque el conservador se selecciona del grupo que consiste de metilparabeno, propilparabeno, benzoato de sodio, sorbato de potasio, y cualesquiera de las combinaciones de éstos y está presente en una cantidad de 0.01% en peso hasta alrededor de 5% en peso.

21. La composición en polvo de conformidad con la reivindicación 18, caracterizada porque el agente saborizante está presente en una cantidad alrededor de 0.001% en peso hasta alrededor de 1% en peso.

22. La composición en polvo de conformidad con la reivindicación 18, caracterizada porque el agente de solución amortiguadora se selecciona del grupo que consiste de ácido cítrico, citrato de sodio, solución amortiguadora de fosfato, solución amortiguadora de acetato, y cualesquiera de las

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combinaciones de estos y está presente en una cantidad alrededor de 1% en peso hasta alrededor de 20% en peso.

23. La composición en polvo de conformidad con la reivindicación 18, caracterizada porque el agente farmacéuticamente activo además del entecavir se selecciona del grupo que consiste de didanosina, lamivudina, abacavir, adefovir, adefovir dipivoxil, famciclovir, (2R, 4R)-4-(2,6-diamino-9H-purin-9-yl)-2-hidroximetil-1,3-dioxolano (DAPD), proteínas inmunomoduladoras de hepatitis B (EHT 899 de Enzo Biochem), emtricitabina, 1-(2-desoxi-2-fluoro-β-D-arabinofuranosil)timina (FMAU), GLQ-223 (Compuesto A, alfa-tricosantin), epavudina (L-dT), epcitabina (L-dC), ribavirin, tenofovir (PMPA), 2',3'-didesoxi-2',3'-dideshidro-beta-L(-)-5-fluorocitidina [L(-)Fd4C], fluoro L- y D-nucleósidos, inmunomoduladores, y cualesquiera combinaciones de éstos.

24. Un método para preparar una composición líquida farmacéutica para la administración oral que contiene una dosis baja de entecavir, que comprende la etapa de disolución del entecavir y el conservador en una solución que comprende un solvente farmacéuticamente aceptable, caracterizado porque el entecavir está presente en la solución en una cantidad alrededor de 0.001% hasta alrededor de 20% en una base peso/volumen de la solución.

25. El método de conformidad con la reivindicación 24, caracterizado porque el solvente farmacéuticamente aceptable

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X

es agua.

26. El método de conformidad con la reivindicación 24, caracterizado porque comprende además las etapas de:

- (a) disolución de un edulcorante en la solución;
- (b) disolución de un agente amortiguador en la solución; y
- (c) disolución de un agente saborizante en la solución.

27. Un método para preparar un polvo para reconstitución en el momento de uso como una composición farmacéutica líquida para administración oral que contiene una baja dosis de entecavir, caracterizado porque comprende la etapa de mezclar el entecavir con por lo menos un componente adicional seleccionado del grupo que consiste de edulcorante, conservador, agente saborizante, agente de solución amortiguadora, y cualesquiera combinaciones de éstos, en donde se forma el polvo para constitución y donde el entecavir está presente en el polvo para constitución de la composición en una cantidad alrededor de 0.001% en peso a alrededor de 20% en peso.

28. Una composición farmacéutica líquida caracterizada porque comprende:

- alrededor de 0.001% a alrededor de 20% de entecavir;
- alrededor de 10% a alrededor de 85% de edulcorante;
- alrededor 0.001% a alrededor de 0.1% de agente saborizante;
- alrededor de 0.01% a alrededor de 1% de conservador;
- alrededor de 0.01% a alrededor de 5% de agente de solución

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amortiguadora; y

c.s. de solvente farmacéuticamente aceptable,

en donde los porcentajes son sobre una base de peso/volumen.

29. La composición farmacéutica líquida de conformidad con la reivindicación 28, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.003% a alrededor de 10% p/v.

30. La composición farmacéutica líquida de conformidad con la reivindicación 29, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.005% a alrededor de 5% p/v.

31. La composición farmacéutica líquida de conformidad con la reivindicación 30, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.005% a alrededor de 1% p/v.

32. La composición farmacéutica líquida de conformidad con la reivindicación 28, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.005% p/v.

33. La composición farmacéutica líquida de conformidad con la reivindicación 28, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.02% p/v.

34. Un polvo para constitución en el momento de uso como una composición farmacéutica líquida, caracterizado porque comprende:

alrededor de 0.001% en peso a alrededor de 20% en peso

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de entecavir;

alrededor de 70% en peso a alrededor de 90% en peso de edulcorante;

alrededor de 0.001% en peso a alrededor de 1% en peso de agente saborizante;

alrededor de 0.01% en peso a alrededor de 5% en peso de conservador; y

alrededor de 1% en peso a alrededor de 20% en peso de agente de solución amortiguadora,

en donde los porcentajes están basados en el peso total de la composición en polvo.

35. La composición en polvo de conformidad con la reivindicación 34, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.003% en peso a alrededor de 10% en peso basado en el peso total de la composición en polvo.

36. La composición en polvo de conformidad con la reivindicación 35, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.005% en peso a alrededor de 5% en peso basado en el peso total de la composición en polvo.

37. La composición en polvo de conformidad con la reivindicación 36, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.005% en peso a alrededor de 1% en peso basado en el peso total de la

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composición en polvo.

38. La composición en polvo de conformidad con la reivindicación 34, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.013% en peso basado en el peso total de la composición en polvo.

39. La composición en polvo de conformidad con la reivindicación 34, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.05% en peso basado en el peso total de la composición en polvo.

40. La composición en polvo de conformidad con la reivindicación 34, caracterizada porque el entecavir está presente en una cantidad alrededor de 0.11% en peso basado en el peso total de la composición en polvo.

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RESUMEN DE LA INVENCION

La presente invención proporciona composiciones farmacéuticas líquidas, que tienen una baja dosis de entecavir. En una modalidad de la presente invención, la composición líquida de entecavir es una composición lista para usar que está formulada para ser estable y de sabor agradable. En una segunda modalidad de la presente invención, la composición líquida de entecavir se formula de una composición en polvo en el momento de uso. Las composiciones de baja dosis de entecavir también pueden incluir por lo menos un componente seleccionado de edulcorante, conservador, agente saborizante, agente amortiguador, o combinaciones de estos. Las composiciones líquidas de entecavir también pueden formularse en combinación con otros agentes farmacéuticamente activos.

PATENT COOPERATION TREATY

GY003-WO-P  
SI

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:  
STEPHEN B. DAVIS  
BRISTOL-MYERS SQUIBB COMPANY  
POST BOX 4000  
PRINCETON, NJ 08543-4000

PCT

NOTIFICATION OF TRANSMITTAL OF  
INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing  
(day/month/year)

21 MAY 2004

Applicant's or agent's file reference

GY103 PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US03/10371

International filing date (day/month/year)

03 April 2003 (03.04.2003)

Priority date (day/month/year)

08 April 2002 (08.04.2002)

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Mail Stop PCT, Attn: IPEA/US  
Commissioner for Patents  
P.O. Box 1430  
Alexandria, Virginia 22313-1430

Facsimile No. (703) 305-3230

Form PCT/IPEA/416 (July 1992)

Authorized officer

*Robert Bell-Harris*  
Deputy Judge

Telephone No. 571/272-1600

RECEIVED

BMS PATENT LAW

MAY 28 2004

Docketed Item *NO SIPE*

Due Date

Attorney *S. Davis*

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                               |                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| Applicant's or agent's file reference<br><b>GY103 PCT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |                                                                     |
| International application No.<br><b>PCT/US03/10371</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | International filing date (day/month/year)<br><b>03 April 2003 (03.04.2003)</b>                                               | Priority date (day/month/year)<br><b>08 April 2002 (08.04.2002)</b> |
| International Patent Classification (IPC) or national classification and IPC<br><b>IPC(7): A61K 9/36, 9/48 and US Cl.: 514/261; 424/451</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                               |                                                                     |
| Applicant<br><b>BRISTOL-MYERS SQUIBB COMPANY</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                               |                                                                     |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p>                                                                                                                                         |                                                                                                                               |                                                                     |
| <p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p> |                                                                                                                               |                                                                     |
| Date of submission of the demand<br><b>06 November 2003 (06.11.2003)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Date of completion of this report<br><b>03 May 2004 (03.05.2004)</b>                                                          |                                                                     |
| Name and mailing address of the IPEA/US<br>Mail Stop PCT, Attn: IPEA/US<br>Commissioner for Patents<br>P.O. Box 1430<br>Alexandria, Virginia 22313-1430<br>Facsimile No. (703) 305-3230                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Authorized officer<br><i>Valerie Bell-Harris</i><br>Donna Riggs<br>Telephone No. (571) 272-1600                               |                                                                     |

## I. Basis of the report

## 1. With regard to the elements of the international application:\*

- ☒ the international application as originally filed.
- ☒ the description:  
pages 1-14 as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_.
- ☒ the claims:  
pages 15-19 as originally filed  
pages NONE, as amended (together with any statement) under Article 19  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_.
- ☐ the drawings:  
pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_.
- ☐ the sequence listing part of the description:  
pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_.

## 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

## 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\* Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

**V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

|                               |                    |     |
|-------------------------------|--------------------|-----|
| Novelty (N)                   | Claims <u>NONE</u> | YES |
|                               | Claims <u>1-40</u> | NO  |
| Inventive Step (IS)           | Claims <u>NONE</u> | YES |
|                               | Claims <u>1-40</u> | NO  |
| Industrial Applicability (IA) | Claims <u>1-40</u> | YES |
|                               | Claims <u>NONE</u> | NO  |

**2. CITATIONS AND EXPLANATIONS**

Claims 1-40 lack novelty under PCT Article 33(2) as being anticipated by Colonna et al. The claims are drawn to a liquid pharmaceutical composition comprising entecavir in a concentration of about 0.001% to about 20% in a solvent and further comprising at least one component selected from a sweetener, preservative, flavoring agent, buffering agent, and pH adjusting agent. Also claimed is a powder for reconstitution at the time of use as a liquid composition. Colonna et al. teach compositions containing low dose entecavir formulated in the form of, *inter alia*, powders, elixirs, solutions or suspensions. Capsule and tablet formulations are prepared to contain about 0.001mg to about 10mg of entecavir. Since the methods of preparing suspensions, solutions and elixirs are well known by one of skill in the art, preparation of the suspension/powders of claims 1-40 would have been obvious to one of skill in the art at the time the invention was made.

NEW CITATIONS

# PATENT COOPERATION TREATY

GY0103-WO-PC  
SS ✓  
COK  
5

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:  
STEPHEN B. DAVIS  
BRISTOL-MYERS SQUIBB COMPANY  
POST BOX 4000  
PRINCETON, NJ 08543-4000

## PCT

### WRITTEN OPINION

(PCT Rule 66)

|                                                                                                                                               |                                                                              |                                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Applicant's or agent's file reference<br><br>GY103 PCT                                                                                        |                                                                              | Date of Mailing (day/month/year) <b>02 MAR 2004</b><br>REPLY DUE within 2 months/days from the above date of mailing ✓ |
| International application No.<br><br>PCT/US03/10371                                                                                           | International filing date (day/month/year)<br><br>03 April 2003 (03.04.2003) | Priority date (day/month/year)<br><br>08 April 2002 (08.04.2002)                                                       |
| International Patent Classification (IPC) or both national classification and IPC<br><br>IPC(7): A61K 9/36, 9/48 and US Cl.: 514/261; 424/451 |                                                                              |                                                                                                                        |
| Applicant<br><br>BRISTOL-MYERS SQUIBB COMPANY                                                                                                 |                                                                              |                                                                                                                        |

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application
3. The applicant is hereby invited to reply to this opinion.
 

**When?** See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also** For an additional opportunity to submit amendments, see Rule 66.4.  
 For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
 For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 08 August 2004 (08.08.2004)

|                                                                                                                                                                                         |                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Name and mailing address of the IPEA/US<br>Mail Stop PCT, Attn: IPEA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Authorized officer<br><i>Valerie B. [Signature]</i><br>Donna J. [Signature]<br>Telephone No. (571) 272-0600 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|

Form PCT/IPEA/408 (cover sheet)(July 1998)

**RECEIVED**  
**ABN'S PATENT LAW**

MAR 04 2004

Docketed Item Written Opn.  
 Due Date 5/2/04  
 Attorney S. Davis

WRITTEN OPINION

International application No.

PCT/US03/10371

I. Basis of the opinion

1. With regard to the elements of the international application:\*

- ☒ the international application as originally filed
- ☒ the description:  
 pages 1-14, as originally filed  
 pages NONE, filed with the demand  
 pages NONE, filed with the letter of \_\_\_\_\_.
- ☒ the claims:  
 pages 15-19, as originally filed  
 pages NONE, as amended (together with any statement) under Article 19  
 pages NONE, filed with the demand  
 pages NONE, filed with the letter of \_\_\_\_\_.
- ☐ the drawings:  
 pages NONE, as originally filed  
 pages NONE, filed with the demand  
 pages NONE, filed with the letter of \_\_\_\_\_.
- ☐ the sequence listing part of the description:  
 pages NONE, as originally filed  
 pages NONE, filed with the demand  
 pages NONE, filed with the letter of \_\_\_\_\_.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."

WRITTEN OPINION

International application No.  
PCT/US03/10371

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

|                               |                    |     |
|-------------------------------|--------------------|-----|
| Novelty (N)                   | Claims <u>NONE</u> | YES |
|                               | Claims <u>1-40</u> | NO  |
| Inventive Step (IS)           | Claims <u>NONE</u> | YES |
|                               | Claims <u>1-40</u> | NO  |
| Industrial Applicability (IA) | Claims <u>1-40</u> | YES |
|                               | Claims <u>NONE</u> | NO  |

2. CITATIONS AND EXPLANATIONS

Claims 1-40 lack novelty under PCT Article 33(2) as being anticipated by Colomo et al. The claims are drawn to a liquid pharmaceutical composition comprising entecavir in a concentration of about 0.001% to about 20% in a solvent and further comprising at least one component selected from a sweetener, preservative, flavoring agent, buffering agent, and pH adjusting agent. Also claimed is a powder for reconstitution at the time of use as a liquid composition. Colomo et al. teach compositions containing low dose entecavir formulated in the form of, *inter alia*, powders, elixirs, solutions or suspensions. Capsule and tablet formulations are prepared to contain about 0.001mg to about 10mg of entecavir. Since the methods of preparing suspensions, solutions and elixirs are well known by one of skill in the art, preparation of the suspension/powders of claims 1-40 would have been obvious to one of skill in the art at the time the invention was made.

NEW CITATIONS

WRITTEN OPINION

International application No.  
PCT/US03/10371

10/1

Supplemental Box  
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

## PCT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

DAVIS, Stephen, B.  
Bristol-Myers Squibb Company  
P.O. Box 4000  
Princeton, NJ 08543-4000  
United States of America

**NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

|                                                                        |                                                            |
|------------------------------------------------------------------------|------------------------------------------------------------|
| Date of mailing (day/month/year)<br>26 May 2003 (26.05.03)             | <b>IMPORTANT NOTIFICATION</b>                              |
| Applicant's or agent's file reference<br>GY103 PCT                     |                                                            |
| International application No.<br>PCT/US03/10371                        |                                                            |
| International publication date (day/month/year)<br>Not yet published   |                                                            |
| International filing date (day/month/year)<br>03 April 2003 (03.04.03) | Priority date (day/month/year)<br>08 April 2002 (08.04.02) |
| Applicant<br><b>BRISTOL-MYERS SQUIBB COMPANY et al</b>                 |                                                            |

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| <u>Priority date</u>     | <u>Priority application No.</u> | <u>Country or regional Office<br/>or PCT receiving Office</u> | <u>Date of receipt<br/>of priority document</u> |
|--------------------------|---------------------------------|---------------------------------------------------------------|-------------------------------------------------|
| 08 April 2002 (08.04.02) | 60/370,674                      | US                                                            | 13 May 2003 (13.05.03)                          |

|                                                                                                                                               |                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| <p>The International Bureau of WIPO<br/>34, chemin des Colombettes<br/>1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 338.89.75</p> | <p>Authorized officer<br/>A. ZOLTANSKI (Fax : 338 89 75)</p> <p>Telephone No. (41-22) 338 8668</p> |
|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|

60  
Page 1 of 2



UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS  
UNITED STATES PATENT AND TRADEMARK OFFICE  
WASHINGTON, D.C. 20231  
www.uspto.gov

| APPLICATION NUMBER | FILING DATE | GRP ART UNIT | FIL FEE RECD | ATTY DOCKET NO | DRAWINGS | TOT CLAIMS | IND CLAIMS |
|--------------------|-------------|--------------|--------------|----------------|----------|------------|------------|
| 60/370,674         | 04/08/2002  |              | 160          | GY0103 (PSP)   |          |            |            |

23914  
STEPHEN B. DAVIS  
BRISTOL-MYERS SQUIBB COMPANY  
PATENT DEPARTMENT  
P O BOX 4000  
PRINCETON, NJ 08543-4000

CONFIRMATION NO. 5902

FILING RECEIPT  
[Barcode]  
"OC000000007985116"

APR 10 2002  
[Signature]

Date Mailed: 04/30/2002

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Divyakant Desai, West Windsor, NJ; ✓  
Daping Li, East Brunswick, NJ; ✓

If Required, Foreign Filing License Granted 04/30/2002

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

Low dose liquid entecavir formulations and use ✓

LICENSE FOR FOREIGN FILING UNDER  
Title 35, United States Code, Section 184  
Title 37, Code of Federal Regulations, 5.11 & 5.15

## **GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

## **NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12; if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PCT Demand Chapter II

Int'l. Application No. PCT/US03/10371

Docket No. GY103 PCT

Express mail mailing label number EV323501082 US

Date of Deposit November 6, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Mail Stop PCT, Alexandria, VA 22313.

Tina Markee

(Typed or printed name of person mailing paper or fee)

Tina Markee

(Signature of person mailing paper or fee)

62<sup>5</sup>

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:  
IPEA/ US

# PCT

## CHAPTER II

### DEMAND

under Article 31 of the Patent Cooperation Treaty.

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

| For International Preliminary Examining Authority use only                                                                                                                                                                                                                |                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| Identification of IPEA                                                                                                                                                                                                                                                    | Date of receipt of DEMAND                                          |
| <b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>                                                                                                                                                                                                          |                                                                    |
| Applicant's or agent's file reference<br>GY103 PCT                                                                                                                                                                                                                        |                                                                    |
| International application No.<br>PCT/US03/10371                                                                                                                                                                                                                           | International filing date (day/month/year)<br>April 03, 2003       |
| (Earliest) Priority date (day/month/year)<br>April 08, 2002                                                                                                                                                                                                               |                                                                    |
| Title of invention<br>LOW DOSE LIQUID ENTECAVIR FORMULATIONS AND USE                                                                                                                                                                                                      |                                                                    |
| <b>Box No. II APPLICANT(S)</b>                                                                                                                                                                                                                                            |                                                                    |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, NJ 08543-4000<br>United States of America | Telephone No.<br>609-252-4000                                      |
|                                                                                                                                                                                                                                                                           | Facsimile No.<br>609-252-4526                                      |
|                                                                                                                                                                                                                                                                           | Teleprinter No.                                                    |
|                                                                                                                                                                                                                                                                           | Applicant's registration No. with the Office                       |
| State (that is, country) of nationality:<br>United States of America                                                                                                                                                                                                      | State (that is, country) of residence:<br>United States of America |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)<br>DESAI, Divyakant<br>19 Greenfield Dr., North<br>West Windsor, NJ 08550<br>United States of America    |                                                                    |
| State (that is, country) of nationality:<br>US                                                                                                                                                                                                                            | State (that is, country) of residence:<br>US                       |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)<br>LI, Danping<br>10 Bearsley Dr.<br>East Brunswick, NJ 08816<br>United States of America                |                                                                    |
| State (that is, country) of nationality:<br>US                                                                                                                                                                                                                            | State (that is, country) of residence:<br>US                       |
| <input type="checkbox"/> Further applicants are indicated on a continuation sheet.                                                                                                                                                                                        |                                                                    |

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*DAVIS, Stephen B.  
Bristol-Myers Squibb Company  
P.O. Box 4000  
Princeton, NJ 08543-4000  
United States of America

Telephone No.

609-252-4338

Facsimile No.

609-252-4526

Teleprinter No.

Agent's registration No. with the Office

26,693

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**

Statement concerning amendments:\*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

## Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- |                                                                          |   |          |
|--------------------------------------------------------------------------|---|----------|
| 1. translation of international application                              | : | 0 sheets |
| 2. amendments under Article 34                                           | : | 0 sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | 0 sheets |
| 4. copy (or, where required, translation) of statement under Article 19  | : | 0 sheets |
| 5. letter                                                                | : | 0 sheets |
| 6. other (specify)                                                       | : | 0 sheets |

For International Preliminary Examining Authority use only

|          |              |
|----------|--------------|
| received | not received |
|----------|--------------|

|                          |                          |
|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |

The demand is also accompanied by the item(s) marked below:

- |                                                                                          |                                                                        |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| 1. <input checked="" type="checkbox"/> fee calculation sheet                             | 5. <input type="checkbox"/> statement explaining lack of signature     |
| 2. <input type="checkbox"/> original separate power of attorney                          | 6. <input type="checkbox"/> sequence listing in computer readable form |
| 3. <input type="checkbox"/> original general power of attorney                           | 7. <input type="checkbox"/> other (Certification for POA):             |
| 4. <input type="checkbox"/> copy of general power of attorney; reference number, if any: |                                                                        |

## Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Stephen B Davis, Agent  
Stephen B. Davis

Date: Nov 6, 2003

## For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

## For International Bureau use only

Demand received from IPEA on:

## PCT

## FEE CALCULATION SHEET

## Annex to the Demand

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                           |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| International application No. <b>PCT/US03/10371</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | For International Preliminary Examining Authority use only                                                                                                                |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| Applicant's or agent's file reference <b>GY103 PCT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Date stamp of the IPEA                                                                                                                                                    |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| Applicant<br><b>Bristol-Myers Squibb Company</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                           |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| <b>CALCULATION OF PRESCRIBED FEES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                           |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| 1. Preliminary examination fee .....                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>490.00</b>                                                                                                                                                             | <div style="border: 1px solid black; padding: 2px; display: inline-block;">P</div> |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| 2. Handling fee ( <i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i> ) .....                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>146.00</b>                                                                                                                                                             | <div style="border: 1px solid black; padding: 2px; display: inline-block;">H</div> |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| 3. Total of prescribed fees<br>Add the amounts entered at P and H<br>and enter total in the TOTAL box .....                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <div style="border: 1px solid black; padding: 5px; display: inline-block;"> <b>636.00</b> </div>                                                                          |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| <div style="border: 1px solid black; padding: 2px; display: inline-block;">TOTAL</div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                           |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| <b>MODE OF PAYMENT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                           |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)<br/> <input type="checkbox"/> cheque<br/> <input type="checkbox"/> postal money order<br/> <input type="checkbox"/> bank draft         </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> cash<br/> <input type="checkbox"/> revenue stamps<br/> <input type="checkbox"/> coupons<br/> <input type="checkbox"/> other (specify):         </td> </tr> </table>                                                                                                                                                                        |                                                                                                                                                                           |                                                                                    | <input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)<br><input type="checkbox"/> cheque<br><input type="checkbox"/> postal money order<br><input type="checkbox"/> bank draft                                                                                                           | <input type="checkbox"/> cash<br><input type="checkbox"/> revenue stamps<br><input type="checkbox"/> coupons<br><input type="checkbox"/> other (specify):                 |
| <input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)<br><input type="checkbox"/> cheque<br><input type="checkbox"/> postal money order<br><input type="checkbox"/> bank draft                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> cash<br><input type="checkbox"/> revenue stamps<br><input type="checkbox"/> coupons<br><input type="checkbox"/> other (specify):                 |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| <b>AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT</b><br><i>(This mode of payment may not be available at all IPEAs)</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                           |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |
| <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Authorization to charge the total fees indicated above.<br/><br/> <input checked="" type="checkbox"/> <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit.)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.         </td> <td style="width: 50%; vertical-align: top;">           IPEA/ <u>US</u><br/><br/>           Deposit Account No.: <u>19.3880</u><br/><br/>           Date: <u>Nov 6, 2003</u><br/><br/>           Name: <u>Stephen B. Davis</u><br/><br/>           Signature: <u>Stephen B. Davis</u> </td> </tr> </table> |                                                                                                                                                                           |                                                                                    | <input type="checkbox"/> Authorization to charge the total fees indicated above.<br><br><input checked="" type="checkbox"/> <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit.)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. | IPEA/ <u>US</u><br><br>Deposit Account No.: <u>19.3880</u><br><br>Date: <u>Nov 6, 2003</u><br><br>Name: <u>Stephen B. Davis</u><br><br>Signature: <u>Stephen B. Davis</u> |
| <input type="checkbox"/> Authorization to charge the total fees indicated above.<br><br><input checked="" type="checkbox"/> <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit.)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.                                                                                                                                                                                                                                                                                                                                                                                                                           | IPEA/ <u>US</u><br><br>Deposit Account No.: <u>19.3880</u><br><br>Date: <u>Nov 6, 2003</u><br><br>Name: <u>Stephen B. Davis</u><br><br>Signature: <u>Stephen B. Davis</u> |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                           |

# RECEIVED PCT COOPERATION TREATY

From **RMS PATENT LAW**

To:  
STEPHEN B. DAVIS  
BRISTOL-MYERS SQUIBB COMPANY  
POST BOX 4000  
PRINCETON, NJ 08542-4000

Docketed Item

Due Date

Attorney

AUG 15 2003  
15-105 ✓  
11/13/03  
SBQ

PCT

## NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing  
(day/month/year)

13 AUG 2003

Applicant's or agent's file reference  
GY103 PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.  
PCT/US03/10371

International filing date  
(day/month/year)

03 April 2003 (03.04.2003)

Applicant  
BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes  
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

### 4. Reminders

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US  
Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
Facsimile No. (703) 305-3230

Authorized officer

Valerie Bell-Harrington  
Deena Jagan

Telephone No. (703) 308-1235

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:  
STEPHEN B. DAVIS  
BRISTOL-MYERS SQUIBB COMPANY  
POST BOX 4000  
PRINCETON, NJ 08543-4000

## PCT

### NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing  
(day/month/year)

**13 AUG 2003**

Applicant's or agent's file reference  
GY103 PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.  
PCT/U803/10371

International filing date  
(day/month/year)

03 April 2003 (03.04.2003)

Applicant  
BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

**When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

**Where?** Directly to the International Bureau of WIPO, 34, chemin des Colombettes  
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.33

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

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In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US  
Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
Facsimile No. (703) 305-3230

Authorized officer

*Valerie Bell-Harris*  
Deputy Jagon

Telephone No. (703) 308-1235

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                    |                                                                          |                                                                                                                                     |
|----------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Applicant's or agent's file reference<br>GY103 PCT | FOR FURTHER<br>ACTION                                                    | see Notification of Transmittal of International Search Report<br>(Form PCT/ISA/220) as well as, where applicable, item 5<br>below. |
| International application No.<br>PCT/US03/10371    | International filing date (day/month/year)<br>03 April 2003 (03.04.2003) | (Earliest) Priority Date (day/month/year)<br>08 April 2002 (08.04.2002)                                                             |
| Applicant<br>BRISTOL-MYERS SQUIBB COMPANY          |                                                                          |                                                                                                                                     |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

#### 1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐

contained in the international application in written form.

☐

filed together with the international application in computer readable form.

☐

furnished subsequently to this Authority in written form.

☐

furnished subsequently to this Authority in computer readable form.

☐

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,

☒

the text is approved as submitted by the applicant.

☐

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒

the text is approved as submitted by the applicant.

☐

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_

☐

as suggested by the applicant.

☐

because the applicant failed to suggest a figure.

☐

because this figure better characterizes the invention.

☐

None of the figures

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/10371

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/36, 9/48

US CL : 514/261; 424/451

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)

U.S. : 514/261; 424/451

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)  
WEST 2.1, STN, file REG, file MEDICINE, search terms: entecavir, low dose, oral, peroral, enteral, composition.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                         | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | US 2001/0033864 A1 (COLONNO et al.) 25 October 2001 (25.10.2001) see entire document.                                                                                      | 1-40                  |
| A          | MARION et al. Potent Efficacy of Entecavir (BMS0200475) in a Duck Model of Hepatitis B Virus Replication, Antimicrobial Agents and Chemotherapy, January 2002 pages 82-88. | 1-40                  |

☐ 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 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

"Z" document member of the same patent family

Date of the actual completion of the international search

02 June 2003 (02.06.2003)

Date of mailing of the international search report

13 AUG 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1490  
Alexandria, Virginia 22313-1490

Facsimile No. (703)305-3230

Authorized officer

Doris Jagoe

Telephone No. (703) 308-1235

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71  
X

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purpose of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

**What parts of the international application may be amended ?**

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

**When ?** Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

**Where not to file the amendments ?**

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

**How ?** Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

**What documents must/may accompany the amendments ?**

**Letter (Section 205(b)):**

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

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## NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)".

It should not contain any disparaging comments on the international search report or the relevance of citations contained in the report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

### Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT REQUEST

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|         |                                                                                                                                         |                                                                                                           |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| 0       | For receiving Office use only                                                                                                           |                                                                                                           |
| 0-1     | International Application No.                                                                                                           |                                                                                                           |
| 0-2     | International Filing Date                                                                                                               |                                                                                                           |
| 0-3     | Name of receiving Office and "PCT International Application"                                                                            |                                                                                                           |
| 0-4     | Form - PCT/RO/101 PCT Request                                                                                                           |                                                                                                           |
| 0-4-1   | Prepared using                                                                                                                          | PCT-EASY Version 2.92<br>(updated 01.01.2003)                                                             |
| 0-5     | Petition<br>The undersigned requests that the present International application be processed according to the Patent Cooperation Treaty |                                                                                                           |
| 0-6     | Receiving Office (specified by the applicant)                                                                                           | United States Patent and Trademark Office (USPTO) (RO/US)                                                 |
| 0-7     | Applicant's or agent's file reference                                                                                                   | GY103 PCT                                                                                                 |
| I       | Title of Invention                                                                                                                      | LOW DOSE LIQUID ENTECAVIR FORMULATIONS AND USE                                                            |
| II      | Applicant                                                                                                                               |                                                                                                           |
| II-1    | This person is:                                                                                                                         | applicant only                                                                                            |
| II-2    | Applicant for                                                                                                                           | all designated States except US                                                                           |
| II-4    | Name                                                                                                                                    | BRISTOL-MYERS SQUIBB COMPANY                                                                              |
| II-5    | Address:                                                                                                                                | P. O. Box 4000<br>Route 206 and Provinceline Road<br>Princeton, NJ 08543-4000<br>United States of America |
| II-6    | State of nationality                                                                                                                    | US                                                                                                        |
| II-7    | State of residence                                                                                                                      | US                                                                                                        |
| II-8    | Telephone No.                                                                                                                           | 609-252-4000                                                                                              |
| II-9    | Facsimile No.                                                                                                                           | 609-252-4526                                                                                              |
| III-1   | Applicant and/or inventor                                                                                                               |                                                                                                           |
| III-1-1 | This person is:                                                                                                                         | applicant and inventor                                                                                    |
| III-1-2 | Applicant for                                                                                                                           | US only                                                                                                   |
| III-1-4 | Name (LAST, First)                                                                                                                      | DESAI, Divyakant                                                                                          |
| III-1-5 | Address:                                                                                                                                | 19 Greenfield Dr., North<br>West Windsor, NJ 08550<br>United States of America                            |
| III-1-6 | State of nationality                                                                                                                    | US                                                                                                        |
| III-1-7 | State of residence                                                                                                                      | US                                                                                                        |

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|         |                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| III-2   | <b>Applicant and/or inventor</b>                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| III-2-1 | This person is:                                                                                                                                                                                                          | applicant and inventor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| III-2-2 | Applicant for                                                                                                                                                                                                            | US only                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| III-2-4 | Name (LAST, First)                                                                                                                                                                                                       | LI, Daping                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| III-2-5 | Address:                                                                                                                                                                                                                 | 10 Bearsley Dr.<br>East Brunswick, NJ 08816<br>United States of America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| III-2-6 | State of nationality                                                                                                                                                                                                     | US                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| III-2-7 | State of residence                                                                                                                                                                                                       | US                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| IV-1    | <b>Agent or common representative; or address for correspondence</b><br>The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: | agent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| IV-1-1  | Name (LAST, First)                                                                                                                                                                                                       | DAVIS, Stephen, B.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| IV-1-2  | Address:                                                                                                                                                                                                                 | Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, NJ 08543-4000<br>United States of America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| IV-1-3  | Telephone No.                                                                                                                                                                                                            | 609-252-4338                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| IV-1-4  | Facsimile No.                                                                                                                                                                                                            | 609-252-4526                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| IV-1-5  | Agent's registration No.                                                                                                                                                                                                 | 26,693                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| IV-2    | <b>Additional agent(s)</b>                                                                                                                                                                                               | additional agent(s) with same address as first named agent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| IV-2-1  | Name(s)                                                                                                                                                                                                                  | GIBBONS, Maureen(44,121); ALGIERI, Aldo(31,697); BABAJKO, Suzanne(32,880); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen(46,652); DUBOFF, Samuel(25,969); HERMENAUE, Ronald(34,620); KLEIN, Christopher(34,363); LANGE, Keith(44,201); MAKUJINA, Shah(41,174); PATEL, Rana(41,412); PROVOOST, Jonathan(44,292); RODNEY, Burton(22,076); RYAN, Richard(30,491); SHER, Audrey(39,024); PEIST, Kenneth(45,006); O'BRIEN, Maureen(42,043); BELFIELD, Jing(45,914); VANATTEN, Mary, K.(39,408); GOLIAN, Paul, D.(42,591); VOLLES, Warren(33,810); BAKAM, Deanna(45,266); DUNCAN, Laurelee(44,096); KORSER, Elliot(32,705); LAMERDIN, John(44,858) |

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|               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>V</b>      | <b>Designation of States</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>V-1</b>    | <b>Regional Patent</b><br>(other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>AP:</b> GH GM KE LS MW MZ SD SL SZ TZ UG ZM<br><b>ZW</b> and any other State which is a Contracting State of the Harare Protocol and of the PCT<br><b>EA:</b> AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT<br><b>EP:</b> AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT<br><b>OA:</b> BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT |
| <b>V-2</b>    | <b>National Patent</b><br>(other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&amp;LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW</b>                                                                                                                                                                                                                                                                                                                                                   |
| <b>V-5</b>    | <b>Precautionary Designation Statement</b><br><br>In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>V-6</b>    | <b>Exclusion(s) from precautionary designations</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>NONE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>VI-1</b>   | <b>Priority claim of earlier national application</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>VI-1-1</b> | <b>Filing date</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>08 April 2002 (08.04.2002)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>VI-1-2</b> | <b>Number</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>60/370,674</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>VI-1-3</b> | <b>Country</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>US</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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|        |                                                                                                                                                                                                       |                                                                   |                                    |
|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|------------------------------------|
| VI-2   | <b>Priority document request</b><br>The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): | <b>VI-1</b>                                                       |                                    |
| VII-1  | <b>International Searching Authority Chosen</b>                                                                                                                                                       | <b>United States Patent and Trademark Office (USPTO) (ISA/US)</b> |                                    |
| VIII   | <b>Declarations</b>                                                                                                                                                                                   | <b>Number of declarations</b>                                     |                                    |
| VIII-1 | Declaration as to the identity of the inventor                                                                                                                                                        | -                                                                 |                                    |
| VIII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent                                                                              | -                                                                 |                                    |
| VIII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application                                                                  | -                                                                 |                                    |
| VIII-4 | Declaration of inventorship (only for the purposes of the designation of the United States of America)                                                                                                | -                                                                 |                                    |
| VIII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty                                                                                                                        | -                                                                 |                                    |
| IX     | <b>Check list</b>                                                                                                                                                                                     | <b>number of sheets</b>                                           | <b>electronic file(s) attached</b> |
| IX-1   | Request (including declaration sheets)                                                                                                                                                                | 5                                                                 | -                                  |
| IX-2   | Description                                                                                                                                                                                           | 14                                                                | -                                  |
| IX-3   | Claims                                                                                                                                                                                                | 5                                                                 | -                                  |
| IX-4   | Abstract                                                                                                                                                                                              | 1                                                                 | EZABST00.TXT                       |
| IX-5   | Drawings                                                                                                                                                                                              | 0                                                                 | -                                  |
| IX-7   | TOTAL                                                                                                                                                                                                 | 25                                                                |                                    |
|        | <b>Accompanying items</b>                                                                                                                                                                             | <b>paper document(s) attached</b>                                 | <b>electronic file(s) attached</b> |
| IX-8   | Fee calculation sheet                                                                                                                                                                                 | ✓                                                                 | -                                  |
| IX-9   | Original separate power of attorney                                                                                                                                                                   | ✓                                                                 | -                                  |
| IX-17  | PCT-EASY diskette                                                                                                                                                                                     | -                                                                 | Diskette                           |
| IX-18  | Other (specified):                                                                                                                                                                                    | Certification                                                     | -                                  |
| IX-19  | Figure of the drawings which should accompany the abstract                                                                                                                                            |                                                                   |                                    |
| IX-20  | Language of filing of the international application                                                                                                                                                   | English                                                           |                                    |
| X-1    | Signature of applicant, agent or common representative                                                                                                                                                | <i>Stephen B Davis</i>                                            |                                    |
| X-1-1  | Name (LAST, First)                                                                                                                                                                                    | DAVIS, Stephen, B.                                                |                                    |

## FOR RECEIVING OFFICE USE ONLY

|        |                                                                   |  |
|--------|-------------------------------------------------------------------|--|
| 10-1   | Date of actual receipt of the purported international application |  |
| 10-2   | Drawings:                                                         |  |
| 10-2-1 | Received                                                          |  |
| 10-2-2 | Not received                                                      |  |

## PCT REQUEST

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|      |                                                                                                                                         |        |
|------|-----------------------------------------------------------------------------------------------------------------------------------------|--------|
| 10-3 | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application |        |
| 10-4 | Date of timely receipt of the required corrections under PCT Article 11(2)                                                              |        |
| 10-5 | International Searching Authority                                                                                                       | ISA/US |
| 10-6 | Transmittal of search copy delayed until search fee is paid                                                                             |        |

## FOR INTERNATIONAL BUREAU USE ONLY

|      |                                                                |  |
|------|----------------------------------------------------------------|--|
| 11-1 | Date of receipt of the record copy by the International Bureau |  |
|------|----------------------------------------------------------------|--|

## PCT (ANNEX - FEE CALCULATION SHEET)

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GY103 PCT

(This sheet is not part of and does not count as a sheet of the International application)

|         |                                                               |                                                           |
|---------|---------------------------------------------------------------|-----------------------------------------------------------|
| 0       | For receiving Office use only                                 |                                                           |
| 0-1     | International Application No.                                 |                                                           |
| 0-2     | Date stamp of the receiving Office                            |                                                           |
| 0-4     | Form - PCT/ROH/01 (Annex)                                     |                                                           |
| 0-4-1   | PCT Fee Calculation Sheet Prepared using                      | PCT-EASY Version 2.92<br>(updated 01.01.2003)             |
| 0-9     | Applicant's or agent's file reference                         | GY103 PCT                                                 |
| 2       | Applicant                                                     | BRISTOL-MYERS SQUIBB COMPANY, et al.                      |
| 12      | Calculation of prescribed fees                                | fee amount/multiplier      Total amounts (USD)            |
| 12-1    | Transmittal fee T                                             | ⇒ 240                                                     |
| 12-2-1  | Search fee S                                                  | ⇒ 700                                                     |
| 12-2-2  | International search to be carried out by                     | US                                                        |
| 12-3    | International fee                                             |                                                           |
|         | Basic fee (first 30 sheets) b1                                | 407                                                       |
| 12-4    | Remaining sheets                                              | 0                                                         |
| 12-5    | Additional amount (X) b2                                      | 9                                                         |
| 12-6    | Total additional amount                                       | 0                                                         |
| 12-7    | b1 + b2 = B                                                   | 407                                                       |
| 12-8    | Designation fees                                              |                                                           |
|         | Number of designations contained in International application | 95                                                        |
| 12-9    | Number of designation fees payable (maximum 5)                | 5                                                         |
| 12-10   | Amount of designation fee (X) b3                              | 88                                                        |
| 12-11   | Total designation fees D                                      | 440                                                       |
| 12-12   | PCT-EASY fee reduction R                                      | -125                                                      |
| 12-13   | Total International fee (B+D-R) I                             | ⇒ 722                                                     |
| 12-14   | Fee for priority document                                     |                                                           |
|         | Number of priority documents requested                        | 1                                                         |
| 12-15   | Fee per document (X) b4                                       | 20                                                        |
| 12-16   | Total priority document fee P                                 | ⇒ 20                                                      |
| 12-17   | TOTAL FEES PAYABLE (T+S+I+P)                                  | ⇒ 1,682                                                   |
| 12-19   | Mode of payment                                               | authorization to charge deposit account                   |
| 12-20   | Deposit account instructions                                  |                                                           |
|         | The receiving Office:                                         | United States Patent and Trademark Office (USPTO) (RO/US) |
| 12-20-1 | Authorization to charge the total fees indicated above.       | ✓                                                         |

## PCT (ANNEX - FEE CALCULATION SHEET)

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|         |                                                                                                     |                                              |
|---------|-----------------------------------------------------------------------------------------------------|----------------------------------------------|
| 12-20-2 | Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. | ✓                                            |
| 12-20-3 | Authorization to charge the fee for priority document.                                              | ✓                                            |
| 12-21   | Deposit account No.                                                                                 | 19-3880                                      |
| 12-22   | Date                                                                                                | 03 April 2003 (03.04.2003)                   |
| 12-23   | Name and signature                                                                                  | DAVIS, Stephen, B.<br><i>Stephen B Davis</i> |

## VALIDATION LOG AND REMARKS

|        |                                 |                                                                                                   |
|--------|---------------------------------|---------------------------------------------------------------------------------------------------|
| 13-2-7 | Validation messages<br>Contents | Green?<br>The international application contains no drawings. Please verify.                      |
| 13-2-8 | Validation messages<br>Payment  | Green?<br>Please ensure that you have a valid deposit account with the receiving Office selected. |

PCT

Original (for SUBMISSION) - printed on 03.04.2003 09:30:02 AM

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**PCT-EASY INFORMATION SHEET**

(For applicant use only, DO NOT submit this sheet with the International application)

**VALIDATION LOG**

|        |                                                                                                           |
|--------|-----------------------------------------------------------------------------------------------------------|
| Green? | <b>Contents</b><br>The International application contains no drawings. Please verify.                     |
| Green? | <b>Payment</b><br>Please ensure that you have a valid deposit account with the receiving Office selected. |

Before submitting the International Application, please carefully verify that:

- the information contained on printed Request form is correct;
- Box X of the Request form and item 12-23 of the Annex to the Request form have been signed;
- all elements of the International application as indicated in Boxes VIII and IX of the Request form have been attached; and,
- the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

**ATTENTION**

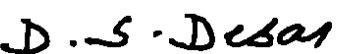
DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

1  
- . . Liquid pharmaceutical compositions are provided having a low dose of entecavir. In one embodiment of the present invention, the liquid entecavir composition is a ready-to-use composition that is formulated to be both stable and palatable. In a second embodiment of the present invention, the liquid entecavir composition is formulated from a powder composition at the time of use. The low dose entecavir compositions may also include at least one component selected from sweetener, preservative, flavoring agent, buffering agent, or combination thereof. The liquid entecavir compositions may also be formulated in combination with other pharmaceutically active agents.

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## PCT POWER OF ATTORNEY

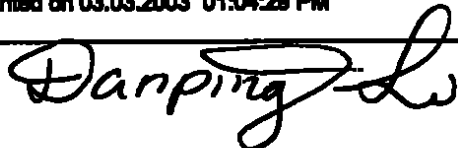
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|       |                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0-1   | PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 90.4) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 0-1-1 | Prepared using                                                                                                     | PCT-EASY Version 2.92<br>(updated 01.01.2003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 1     | The undersigned applicant(s)                                                                                       | DESAI, Divyakant; LI, Danping                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 1-1-1 | hereby appoints (appoint) the following person                                                                     | DAVIS, Stephen, B.; GIBBONS, Maureen; ALGIERI, Aldo; BABAJKO, Suzanne; BUCHHOLZ, Briana; D'AMICO, Stephen; DUBOFF, Samuel; HERMENAUE, Ronald; KLEIN, Christopher; LANGE, Keith; MAKUJINA, Shah; PATEL, Rena; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; PEIST, Kenneth; O'BRIEN, Maureen; BELFIELD, Jing; VANATTEN, Mary, K.; GOLIAN, Paul, D.; VOLLES, Warren; BAXAM, Deanna; DUNCAN, Laurelee; KORSER, Elliot; LAMERDIN, John<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, NJ 08543-4000<br>United States of America |
| 1-2   | as                                                                                                                 | agent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 1-3   | to represent the undersigned before                                                                                | all the competent International Authorities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 1-4   | In connection with the International application identified below:                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 1-4-1 | Title of the invention                                                                                             | LOW DOSE LIQUID ENTECAVIR FORMULATIONS AND USE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 1-4-2 | Applicant's or agent's file reference                                                                              | GY103 PCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 1-4-3 | International application number (if already available)                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 1-4-4 | filed with the following Office as receiving Office                                                                | United States Patent and Trademark Office (USPTO) (RO/US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 1-5   | and to make or receive payments on behalf of the undersigned.                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 2-2   | Signature of applicant<br>      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 2-2-1 | Name                                                                                                               | DESAI, Divyakant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

## PCT POWER OF ATTORNEY

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GY 03 PCT

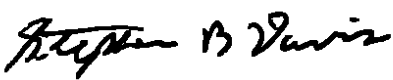
|       |                        |                                                                                    |
|-------|------------------------|------------------------------------------------------------------------------------|
| 2-3   | Signature of applicant |  |
| 2-3-1 | Name                   | LI, Danping                                                                        |
| 3     | Date                   | 03 March 2003 (03.03.2003)                                                         |

## PCT POWER F ATTORNEY

1/2

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|       |                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------|--------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0-1   | PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 90.4) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 0-1-1 | Prepared using                                                                                                     | PCT-EASY Version 2.92<br>(updated 01.01.2003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 1     | The undersigned applicant(s)                                                                                       | BRISTOL-MYERS SQUIBB COMPANY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 1-1-1 | hereby appoints (appoint) the following person                                                                     | DAVIS, Stephen, B.; GIBBONS, Maureen; ALGIERI, Aldo; BABAJKO, Suzanne; BUCHHOLZ, Briana; D'AMICO, Stephen; DUBOFF, Samuel; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; MAKUJINA, Shah; PATEL, Rena; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; PEIST, Kenneth; O'BRIEN, Maureen; BELFIELD, Jing; VANATTEN, Mary, K.; GOLIAN, Paul, D.; VOLLES, Warren; BAXAM, Deanna; DUNCAN, Laurelee; KORSEN, Elliot; LAMERDIN, John<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, NJ 08543-4000<br>United States of America |
| 1-2   | as                                                                                                                 | agent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 1-3   | to represent the undersigned before                                                                                | all the competent International Authorities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 1-4   | In connection with the International application identified below:                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 1-4-1 | Title of the invention                                                                                             | LOW DOSE LIQUID ENTECAVIR FORMULATIONS AND USE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 1-4-2 | Applicant's or agent's file reference                                                                              | GY103 PCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 1-4-3 | International application number (if already available)                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 1-4-4 | filed with the following Office as receiving Office                                                                | United States Patent and Trademark Office (USPTO) (RO/US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 1-5   | and to make or receive payments on behalf of the undersigned.                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 2-1   | Signature of applicant                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 2-1-1 | Name                                                                                                               | BRISTOL-MYERS SQUIBB COMPANY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 2-1-2 | Name of signatory                                                                                                  | Stephen B. Davis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 2-1-3 | Capacity                                                                                                           | Senior Patent Counsel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

**PCT POWER OF ATTORNEY**

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03.03.2003 PCT

|   |      |                            |
|---|------|----------------------------|
| 3 | Date | 03 March 2003 (03.03.2003) |
|---|------|----------------------------|

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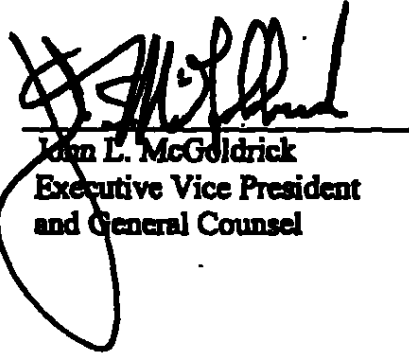
CERTIFICATION

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Suzanne Babajko  
Stephen B. Davis  
Blair Q. Ferguson  
John M. Kilcoyne  
Christopher Klein  
David Morse  
Richard Ryan

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 22<sup>nd</sup> day of May 2002.

  
John L. McGoldrick  
Executive Vice President  
and General Counsel

  
Secretary

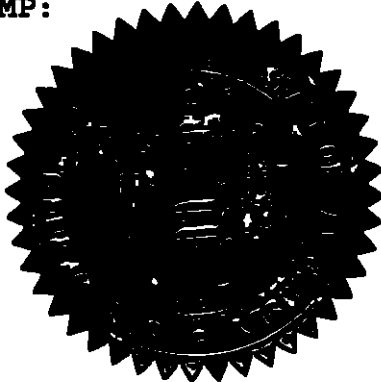
## APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:  
MARIA CASTALDO
3. ACTING IN THE CAPACITY OF:  
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:  
MARIA CASTALDO, NOTARY

## CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 7TH DAY OF SEPTEMBER 2004
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A207412
9. SEAL/STAMP:
10. SIGNATURE

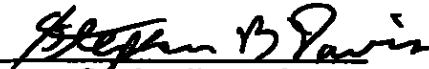


A handwritten signature in cursive script, reading "John E. McCormac".

GY103

AFFIDAVIT

I, **Stephen B. Davis**, Senior Patent Counsel, Patent Department,  
**BRISTOL-MYERS SQUIBB COMPANY**, do hereby certify that this is  
a notarized true and accurate assignment signed by the inventors.



Stephen B. Davis  
Senior Patent Counsel

STATE OF NEW JERSEY     )  
                                          )  
COUNTY OF MERCER     )

Subscribed and sworn to before me this

27<sup>th</sup> day of August, 2004



Maria Castaldo  
Notary Public of New Jersey  
My commission expires October 6, 2008

SEAL



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
ASSISTANT SECRETARY AND COMMISSIONER  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

89  
[Signature]

APRIL 03, 2003

PTAS

BRISTOL-MYERS SQUIBB COMPANY  
STEPHEN B. DAVIS  
PATENT DEPT.  
PO BOX 4000  
PRINCETON, NJ 08543-4000

**\*700027176A\***

\*700027176A\*

UNITED STATES PATENT AND TRADEMARK OFFICE  
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 04/02/2003

REEL/FRAME: 013534/0601  
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

DESAI, DIVYAKANT

DOC DATE: 03/14/2003

ASSIGNOR:

LI, DANPING

DOC DATE: 03/14/2003

ASSIGNEE:

BRISTOL-MYERS SQUIBB COMPANY  
LAWRENCEVILLE-PRINCETON ROAD  
PRINCETON, NEW JERSEY 08543-4000

SERIAL NUMBER: 60370674  
PATENT NUMBER:

FILING DATE: 04/08/2002  
ISSUE DATE:

JOANN STEWART, EXAMINER  
ASSIGNMENT DIVISION  
OFFICE OF PUBLIC RECORDS

04/02/2003  
700027176

GY0103PSP

# 890590

FORM PTO-1585  
(Rev. 8-03)

RECORDATION FORM COVER SHEET

U.S. DEPARTMENT OF COMMERCE  
Patent and Trademark Office

OMB No. 0651-0011 (exp. 4/94)

PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):  
Divyakant Desai & Darping Li

2. Name and address of receiving party(ies)

Name: Bristol-Myers Squibb Company

Internal Address:

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment

☐ Merger

☐ Security Agreement

☐ Change of Name

☐ Other

Street Address: Laurenceville Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

Execution Date: March 14, 2003

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

60/370,674

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Stephen B. Davis

Internal Address: Bristol-Myers Squibb Company

Patent Department

Street Address: P.O. Box 4000

City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) \$ 40

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

19-8880 (in the name of Bristol-Myers Squibb Company)

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Stephen B. Davis

Name of Person Signing  
Reg. No. 25,883

*Stephen B. Davis*  
Signature

April 2, 2003  
Date

☐ Certificate of mailing on reverse side

Total number of pages including cover sheet, attachments, and document: 4

Mail documents to be recorded with required cover sheet information to:  
Commissioner of Patents & Trademarks, Box Assignments  
Washington, D.C. 20231

**ASSIGNMENT**

We,

Divyakant Desai                      residing at              19 Greenfield Drive, North  
West Windsor, New Jersey 08550  
United States of America

Danping Li                              residing at              10 Bearsley Drive  
East Brunswick, New Jersey 08816  
United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

**LOW DOSE LIQUID ENTECAVIR FORMULATIONS AND USE**

invented by us and described in the provisional United States patent application

Application No. 60/370,674, filed April 8, 2002,

Including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

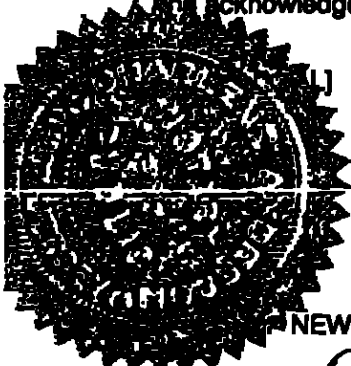
And we hereby agree to communicate to said assignee or its representatives any facts known to be respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 14 day of April, 2003 by \*D. S. Desai  
Divyakant Desai

Signed this 14 day of April, 2003 by \*Danping Li  
Danping Li

STATE OF NEW JERSEY )  
COUNTY OF Middlesex ) ss.

On this day 14 of March, 2003, before me came Divyakant Desai, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.



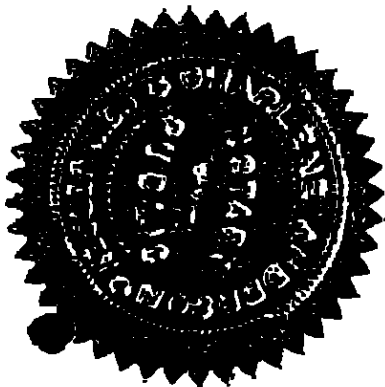
Charlene Anderson  
Notary Public

CHARLENE ANDERSON  
NOTARY PUBLIC OF NEW JERSEY  
MY COMMISSION EXPIRES MAR. 1, 2007

NEW JERSEY )  
COUNTY OF Middlesex ) ss.

On this day 14 of March, 2003, before me came Danping Li, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]



Charlene Anderson  
Notary Public

CHARLENE ANDERSON  
NOTARY PUBLIC OF NEW JERSEY  
MY COMMISSION EXPIRES MAR. 1, 2007

## REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

|                                                                                         | USUARIO | RADICADOR |
|-----------------------------------------------------------------------------------------|---------|-----------|
| <b>PATENTE DE INVENCION</b> ( )                                                         | ( )     | ( )       |
| <b>MODELO DE UTILIDAD</b> ( )                                                           | ( )     | ( )       |
| - Indicación de que se solicita la concesión de una patente.                            | ( )     | ( )       |
| - Datos de identificación del solicitante o de la persona que se presenta la solicitud. | ( )     | ( )       |
| - Descripción de la invención.                                                          | ( )     | ( )       |
| - Dibujos de ser estos pertinentes.                                                     | ( )     | ( )       |
| - Comprobante de Pago de las tasas establecidas.                                        | ( )     | ( )       |

**COMPLETA** ( ) **INCOMPLETA** ( )

**DISEÑO INDUSTRIAL** ( )

|                                                                                                              |     |     |
|--------------------------------------------------------------------------------------------------------------|-----|-----|
| - Indicación de que se solicita el registro de Diseño Industrial                                             | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta la solicitud.                         | ( ) | ( ) |
| - Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | ( ) | ( ) |
| - Comprobante de pago de las tasas establecidas                                                              | ( ) | ( ) |

**COMPLETA** ( ) **INCOMPLETA** ( )

**ESQUEMA DE TRAZADO** ( )

|                                                                                      |     |     |
|--------------------------------------------------------------------------------------|-----|-----|
| - Indicación de que solicita el registro de un Esquema de trazado.                   | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta la solicitud. | ( ) | ( ) |
| - Representación gráfica del esquema de trazado                                      | ( ) | ( ) |
| - Comprobante de pago de las tasas establecidas.                                     | ( ) | ( ) |

**COMPLETA** ( ) **INCOMPLETA** ( )

Firma Responsable:

Fecha:

96  
95



## **SUPERINDUSTRIA Y COMERCIO**

### **MANTENIMIENTO DE PROTOCOLOS**

**Número : 19358**

**Fecha : 07/05/1999**

**Conferido: BRISTOL-MYERS SQUIBB COMPANY**

**Pais : US ESTADOS UNIDOS DE AMERICA**

**Ciudad : 82 PRINCETON, NEW JERSEY**

**Represent: S Sustituir: S Desistir: S**

**No. Radicacion : 99 28346 Clase: 0 Seev: 0 Seac: 0**

---

|   | scncia | Codigo | Ctr | Nombre              |
|---|--------|--------|-----|---------------------|
| 1 | 340    | A      |     | CASTRO DUQUE RAMIRO |
| 2 | 3002   |        |     | GOMEZ MEJIA HECTOR  |

2020  
Bogotá D C

Doctor(a)  
**RAMIRO CASTRO DUQUE**  
Apoderado(a)  
**BRISTOL – MYERS SQUIBB COMPANY**

|                    |                                   |                       |
|--------------------|-----------------------------------|-----------------------|
| <b>REFERENCIA:</b> | <b>Radicación N°</b>              | <b>04-100434</b>      |
|                    | <b>Solicitud internacional</b>    | <b>PCT/US03/10371</b> |
|                    | <b>Fecha inicio fase nacional</b> | <b>08/11/2004</b>     |
|                    | <b>Trámite</b>                    | <b>011</b>            |
|                    | <b>Evento</b>                     | <b>379</b>            |
|                    | <b>Actuación</b>                  | <b>416</b>            |
|                    | <b>Oficio N°</b>                  | <b>1545</b>           |
|                    | <b>Folios</b>                     | <b>001</b>            |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

**Cúmplase**

Dado en Bogotá D C,

**15 OCT. 2004**

  
**ALIX CARMENZA CÉSPEDES DE VERGEL**  
Jefe División de Nuevas Creaciones.

202044