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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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División de Nuevas Creaciones

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54. TITULO

USO DE ATAZANAVIR EN TERAPIA DE VIH

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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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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: BRISTOL - MYERS SQUIBB COMPANY Dirección: P.O. Box 4000, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail:	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____	
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>170.322 TP_1003</u>	
4 INVENTOR (ES) (72)	Nombre: Clifford M. Bechtold Dirección: 17 Streamview Circle, Guilford, CT 06437, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos de América		
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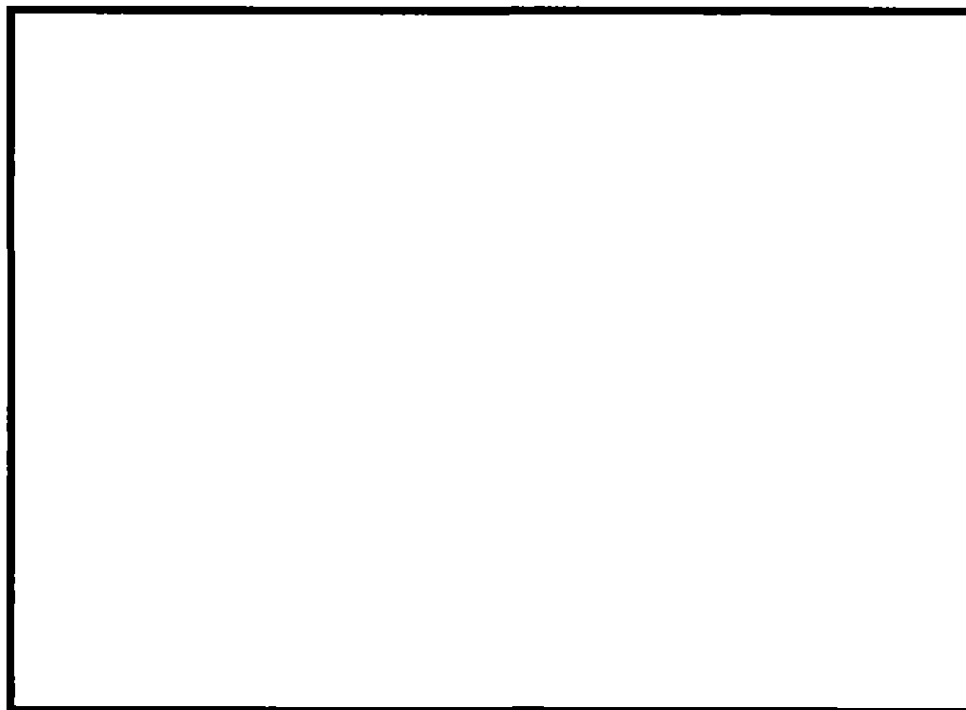
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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

- ☒ 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. 18358
- ☒ 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:



(2) Subjeto la concesión de la patente

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170322 de Bogotá - T.P. 1003 del C.S.J.

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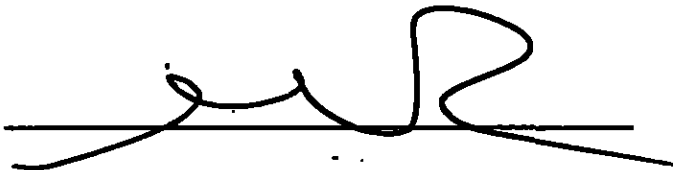
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- (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).
- (72) Inventor: BECHTOLD, Clifford, M., 17 Streamview Circle, Guilford, CT 06437 (US).
- (74) Agent: MORSE, David, M.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).
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(54) Title: USE OF ATAZANAVIR IN HIV THERAPY

(57) Abstract: A method for reducing elevated plasma LDL and/or triglyceride levels in an HIV-infected patient is disclosed. In this method, atazanavir (BMS-232632) can be used to treat HIV infection in patients exhibiting elevated plasma LDL-cholesterol and/or triglyceride levels, can be substituted for an offending HIV protease inhibitor used in such therapy, or can be used in combination with an HIV protease inhibitor metabolized by cytochrome P450 monooxygenase.

USE OF ATAZANAVIR IN HIV THERAPY**REFERENCE TO RELATED APPLICATIONS**

- 5 This application claims the benefit of U.S. Provisional Application Serial Number 60/316,745 filed August 31, 2001.

TECHNICAL FIELD

- 10 This invention relates to methods for reducing certain metabolic side effects in HIV-infected patients, said side effects possibly resulting from the administration of one or more HIV protease inhibitors. More particularly, the invention relates to the substitution of the HIV protease inhibitor, atazanavir, for an HIV protease inhibitor causing elevated blood LDL and/or triglyceride levels or the combination of
15 atazanavir with such other HIV protease inhibitor.

BACKGROUND OF THE INVENTION

- 20 Combination antiretroviral therapy that includes protease inhibitors represents a significant advance in the therapy of HIV infection. HIV protease inhibitors may be combined with HIV inhibitors of other classes, e.g. nucleoside reverse transcriptase inhibitors or non-nucleoside reverse transcriptase inhibitors, or used with other HIV protease inhibitors, often also with nucleoside reverse transcriptase inhibitors and/or non-nucleoside reverse transcriptase inhibitors, in so-called "cocktails".
- 25 Combinations of protease inhibitors have been suggested to combat viral resistance (see, for example, U.S. 6,100,277). The protease inhibitor, ritonavir, has also been disclosed as improving the pharmacokinetics of certain other protease inhibitors when used in combination (see, for example, U.S. 6,037,157).
- 30 A number of HIV protease inhibitors are on the market or under clinical investigation including saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, atazanavir, tipranavir, and lopinavir. Atazanavir (also referred to as BMS-232632) is disclosed in U.S. Patents 5,849,911 and 6,166,004. U.S. Patent 6,087,383 discloses

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the crystalline bisulfate salt of atazanavir. Atazanavir is an azapeptide inhibitor currently in development and undergoing clinical evaluation. It has high potency, a favorable resistance profile, and bioavailability supportive of once-daily oral dosing.

5 Administration of HIV therapy containing HIV protease inhibitors has been found to be accompanied by certain metabolic abnormalities in a significant number of patients, including an elevation in plasma concentrations of low-density lipoproteins (LDL) and triglycerides. Elevation in plasma levels of LDL-cholesterol and triglycerides constitutes a major risk factor for the premature development of
10 atherosclerosis and hypertriglyceridemia, and may also contribute to the development of heart disease and pancreatitis. Individual protease inhibitors differ in their effects on serum lipid profiles, but in general, the current experience is that, to date, all such inhibitors have exhibited this metabolic liability. Ritonavir seems to have the greatest effect, while indinavir, nelfinavir, amprenavir, and saquinavir
15 appear to have somewhat reduced effects on serum lipid levels. The increased LDL-cholesterol and triglyceride levels associated with protease inhibitor use are of growing concern, particularly when regimens containing two or more protease inhibitors are employed.

20 The frequency of hyperlipidemia in HIV-infected patients taking protease inhibitors has been reported to range from 8% to as high as 66% (see *Pharmacotherapy*, 1999, 19:281-298).

One suggested solution to the above problem has been to administer
25 antilipidemic agents to patients having elevated plasma lipid levels resulting from HIV protease inhibitor therapy. However, the most commonly used antilipidemic agents, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, are metabolized by the cytochrome P450 isoenzyme system. Thus, at least with some statins such as simvastatin and lovastatin, antihyperlipidemic efficacy in
30 HIV-infected patients on protease inhibitor therapy may be compromised at standard statin doses.

SUMMARY OF THE INVENTION

In one aspect, there is provided by the present invention a method for reducing elevated plasma LDL-cholesterol and/or triglyceride levels in an HIV-
5 infected patient undergoing therapy with one or more HIV protease inhibitors resulting in such elevated LDL-cholesterol and/or triglyceride levels, comprising substituting in such therapy an HIV-inhibiting and LDL-cholesterol and/or triglyceride reducing amount of atazanavir for the offending HIV protease inhibitor. The reduction in hyperlipidemia is similar to that achieved by use of a statin, but
10 without the side effects seen with this class of lipid-lowering agents. In another aspect, there is provided a method for reducing elevated plasma LDL-cholesterol and/or triglyceride levels in an HIV-infected patient undergoing HIV protease inhibitor therapy which comprises administering to said patient an effective HIV-inhibiting amount of atazanavir in combination with an HIV-inhibiting amount of at
15 least one other HIV protease inhibitor which is metabolized by cytochrome P450 monooxygenase. In yet another aspect, there is provided a method for treating HIV infection in a patient exhibiting elevated plasma LDL-cholesterol and/or triglyceride levels comprising administering to said patient an HIV-inhibiting amount of atazanavir.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the unexpected observation that atazanavir, unlike other HIV protease inhibitors, has no significant effect on plasma LDL-
25 cholesterol and triglyceride levels when administered in normal HIV-inhibiting dosages.

In clinical studies carried out on 98 HIV-positive patients who have taken atazanavir for one year, no increases in plasma LDL-cholesterol or triglycerides were
30 observed. Thus, atazanavir is particularly useful in the treatment of HIV-positive patients who have elevated plasma LDL-cholesterol and/or triglyceride levels. It can be used as monotherapy or as part of a "cocktail" which would include other antiretroviral drugs such as reverse transcriptase inhibitors, non-nucleoside reverse

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transcriptase inhibitors, and other HIV protease inhibitors. In one aspect, then, the present invention provides a method for treating HIV infection in a patient exhibiting elevated plasma LDL-cholesterol and/or triglyceride levels comprising administering to said patient an HIV-inhibiting amount of atazanavir.

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Atazanavir is especially useful in the treatment of HIV-infected patients who have elevated plasma LDL-cholesterol and/or triglyceride levels resulting from antiretroviral therapy with an HIV protease inhibitor.

10 In a Phase II randomized study, the safety and anti-HIV activity of three once daily doses of atazanavir (200 mg, 400 mg and 500 mg) was compared with 750 mg of the protease inhibitor, nelfinavir dosed three times daily. Twenty-one patients received nelfinavir in combination with stavudine and didanosine, while atazanavir was administered both as monotherapy (for two weeks) and then in combination with
15 stavudine and didanosine to 78 treatment-naïve (no prior anti-HIV therapy) patients with HIV viral loads >2000 copies per milliliter (c/mL). Patients in the atazanavir arms showed at least comparable reductions in viral load compared to the nelfinavir-treated patients, but displayed no changes in lipid levels, while after four weeks, those in the nelfinavir arm had an increase in total cholesterol, LDL-cholesterol and
20 triglyceride levels.

In another two-stage, randomized three-arm Phase II study, the antiviral activity and metabolic effects of atazanavir at two different doses (400 mg or 600 mg) was compared to ritonavir, each in combination with saquinavir over 48 weeks.
25 The protease inhibitors were administered in combination with two nucleoside reverse transcriptase inhibitors selected from didanosine, stavudine, lamivudine or zidovudine. The selection of reverse transcriptase inhibitors (used in combination as didanosine + stavudine, stavudine + lamivudine, didanosine + zidovudine, or lamivudine + zidovudine) was based on the patient's phenotypic sensitivity and the
30 physician's choice at the time of administration. The regimens were as follows:

atazanavir 400 mg QD + saquinavir 1200 mg QD + 2 nucleoside reverse transcriptase inhibitors

atazanavir 600 mg QD + saquinavir 1200 mg QD + 2 nucleoside reverse transcriptase inhibitors

5 ritonavir 400 mg BID + saquinavir 400 mg BID + 2 nucleoside reverse transcriptase inhibitors

Patients were anti-retroviral-experienced with a treatment history of receiving a minimum of 24 weeks of a protease inhibitor-containing or non-nucleoside reverse transcriptase inhibitor-containing combination regimen. Stage I was to randomize
10 approximately 75 subjects to assess the safety and antiviral activity of the regimens. Following an initial safety assessment of Stage I, an additional 300 patients were randomized into Stage II to assess the magnitude and duration of reduction of plasma HIV RNA from baseline through week 48. The two atazanavir groups were compared to ritonavir in terms of the mean change in total cholesterol from baseline
15 at week 12. The difference estimates for the pairwise comparisons were -49.1 for the atazanavir 600 mg -ritonavir pair and -28.7 for the atazanavir 400 mg-ritonavir pair. Total cholesterol was not elevated on either of the atazanavir groups. The median changes from baseline at week 12 were -20 mg/dL for atazanavir 600 mg and 5 mg/dL for atazanavir 400 compared to 37 mg/dL for ritonavir. Fractionated
20 cholesterol data were available at baseline and week 12 on approximately 1/2 of the patients. LDL-cholesterol was not elevated over baseline on any atazanavir group.

The two atazanavir groups were compared to ritonavir in terms of the mean change in triglycerides from baseline at week 12. The difference estimates for the
25 pairwise comparisons were -135.9 for atazanavir 600-ritonavir and -155.2 for atazanavir 400 mg-ritonavir. The median changes from baseline at week 12 were 5 mg/dL for atazanavir 600 mg and -14 mg/dL for atazanavir 400 mg compared to 102 mg/dL for ritonavir. The two groups showed similar antiviral efficacy through week 12. This study shows that patients with elevated plasma LDL-cholesterol and
30 triglycerides can be effectively switched to an atazanavir-containing therapy to maintain viral suppression while reducing LDL-cholesterol and triglyceride levels. Thus, the method of the present invention provides an effective and safe alternative to

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statin intervention that can result in additional side effect risks and adversely impact other medications.

Atazanavir can be used alone or in combination with one or more other
5 pharmaceutically active substances that are active against retroviruses, especially HIV. Such other substances may be, for example, inhibitors of reverse transcriptase, e.g. zidovudine, didanosine, stavudine, zalcitabine, or lamivudine, non-nucleoside reverse transcriptase inhibitors such as efavirenz, or other HIV protease inhibitors.

10 Atazanavir is normally obtained as a weak organic base and is commonly converted for pharmaceutical formulation into pharmaceutically acceptable acid addition salts such as those described in U.S. Patent 6,166,004. A most preferred salt form for pharmaceutical compositions is the bisulfate salt described in U.S. Patent 6,087,383.

15 In the process of the present invention, one starts with an HIV-infected patient who has elevated plasma LDL-cholesterol and/or triglyceride levels. In one aspect of the invention, such patient has been or is undergoing antiretroviral therapy with one or more HIV protease inhibitors other than atazanavir and exhibits elevated plasma
20 LDL-cholesterol and/or triglyceride levels. Such other HIV protease inhibitor(s) may be given as monotherapy or as part of an antiretroviral therapy which also includes one or more other antiretroviral drugs such as reverse transcriptase inhibitors or non-nucleoside reverse transcriptase inhibitors. Such candidates, although they may exhibit satisfactory viral suppression, may be of increased risk for hyperlipidemia and
25 premature cardiovascular events.

The term "elevated plasma LDL-cholesterol and triglyceride levels" as used herein is based on the National Cholesterol Education Program (NCEP) clinical practice guidelines for the prevention and management of high cholesterol in adults.
30 In the latest guidelines issued in 2001, plasma levels of >130 mg/dL of LDL-cholesterol and >150 mg/dL of triglycerides are considered elevated or "high". The process of the present invention is particularly useful for those patients having plasma triglyceride levels of >200 mg/dL and for those patients with no risk factors

or previous cardiovascular events having LDL-cholesterol levels of >160 mg/dL. The definition of "elevated" LDL-cholesterol and triglyceride levels may, of course, change in the future as the NCEP continues to evaluate heart attack risk factors. It is intended, then, that the term "elevated LDL-cholesterol and triglyceride levels" as
5 used will be consistent with current NCEP guidelines.

In one of its aspects, the present invention involves discontinuing the offending (the drug responsible for the elevated plasma LDL-cholesterol and/or triglyceride levels) HIV protease inhibitor from the above regimen and substituting
10 therefore an amount of atazanavir which is effective to inhibit HIV and to reduce plasma LDL-cholesterol and/or triglyceride levels.

The dose of atazanavir to be employed depends on such factors as the body weight, age and individual condition of the patient to be treated and the mode of
15 administration. In general dosages of from about 3 mg to approximately 1.6 grams per person per day, divided into 1 to 3 single doses, are suitable. An especially preferred dosage for adult patients is 50-800, more preferably 400-600 and most preferably 400 mg given once daily.

20 The pharmaceutical compositions of atazanavir that may be used in the process of the present invention are those described, for example, in U.S. Patents 6,166,004 and 6,087,383. Suitable forms for oral administration include capsules, tablets and powders for oral suspension.

25 Atazanavir has also been found to be an inhibitor of cytochrome P450 monooxygenase and can improve the pharmacokinetics of drugs metabolized by this enzyme, including particularly other HIV protease inhibitors such as saquinavir, indinavir, nelfinavir, amprenavir, tipranavir and lopinavir. Thus, it acts in a similar way to ritonavir described in U.S. Patent 6,037,157 to increase blood levels of the co-
30 administered HIV protease inhibitor. One notable difference from ritonavir is that atazanavir is employed in combination therapy with other HIV protease inhibitors at its normal therapeutic dose level instead of the sub-therapeutic dose levels used with ritonavir. Because of its potentiating effect on other HIV protease inhibitors which

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are metabolized by cytochrome P450 monooxygenase, use of atazanavir concomitantly with such other HIV protease inhibitors allows reduced dosages of such other HIV protease inhibitors to be used while maintaining the same degree of viral suppression. For example in the Phase II study described above, the dosage of saquinavir could be adjusted from its recommended dosage of 1200 mg 3 times daily to 1200 mg once daily when combined with atazanavir. Atazanavir can be used in combination with other HIV protease inhibitors to reduce LDL-cholesterol and triglyceride levels in AIDS patients undergoing protease inhibitor therapy while still maintaining the desired level of viral suppression.

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The appropriate dose of the HIV protease inhibitor being combined with atazanavir can be determined by the following method which was used for the atazanavir/saquinavir combination:

Atazanavir is a moderate inhibitor of the cytochrome P450 3A enzyme comparable to nelfinavir and indinavir, with a K_i of 2.4 μM . The latter two compounds increase the exposure of saquinavir (dosed at 1200 mg thrice-daily (TID)) by 392 and 364%, respectively, at steady-state. A multiple-dose pharmacology study was completed to evaluate if a similar increase could be expected for the combination of atazanavir and saquinavir. This study showed a greater than 3-fold increase in exposure, due to combination with atazanavir, supporting a 1200 mg once-daily saquinavir dosing, was equivalent to the currently marketed saquinavir regimen of 1200 mg TID. Using a constant dose of atazanavir the range of saquinavir doses were studied to target the saquinavir exposure (AUC (area under the curve) and CMIN (minimum concentration)) similar to those in the literature. Similarly, appropriate dosing of other HIV protease inhibitors to be used in combination with atazanavir can be calculated.

In another aspect, then, the present invention provides a method for reducing plasma LDL-cholesterol and/or triglyceride levels in an HIV-infected patient undergoing HIV protease inhibitor therapy which comprises administering to said patient an effective HIV-inhibiting amount of atazanavir in combination with an

HIV-inhibiting amount of at least one HIV protease inhibitor metabolized by cytochrome P450 monooxygenase.

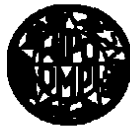
The present invention also provides pharmaceutical compositions comprising
5 an effective HIV-inhibiting amount of atazanavir and an effective HIV-inhibiting
amount of at least one other HIV protease inhibitor which is metabolized by
cytochrome P450 monooxygenase. Compositions in the form of capsules, tablets,
nasal sprays, solutions, powders, granules, emulsions, syrups, suppositories,
liposomes, suspensions, etc. such as those disclosed in U.S. Patent 6,166,004 are
10 suitable for the present invention.

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XCLAIMS

What is claimed is:

- 5 1. A method for reducing elevated plasma LDL and/or triglyceride levels in an HIV-infected patient resulting from therapy with one or more HIV protease inhibitors, comprising substituting an HIV-inhibiting and LDL and/or triglyceride reducing amount of atazanavir for the offending HIV protease inhibitor used in such therapy.
- 10 2. A method for reducing elevated plasma LDL and/or triglyceride levels in an HIV-infected patient undergoing HIV protease therapy which comprises administering to said patient an effective HIV-inhibiting amount of atazanavir in combination with an HIV-inhibiting amount of at least one HIV protease inhibitor
- 15 metabolized by cytochrome P450 monooxygenase.
3. The method of Claim 2 wherein atazanavir is administered in combination with an HIV protease inhibitor selected from saquinavir, indinavir, amprenavir, nelfinavir, tipranavir or lopinavir.
- 20 4. The method of Claim 3 wherein atazanavir is administered in combination with saquinavir.
- 25 5. A method for treating HIV infection in a patient exhibiting elevated plasma LDL-cholesterol and/or triglyceride levels comprising administering to said patient an HIV-inhibiting amount of atazanavir.
- 30

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(57) Abstract: A method for reducing elevated plasma LDL and/or triglyceride levels in an HIV-infected patient is disclosed. In this method, atazanavir (BMS-232632) can be used to treat HIV infection in patients exhibiting elevated plasma LDL-cholesterol and/or triglyceride levels, can be substituted for an offending HIV protease inhibitor used in such therapy, or can be used in combination with an HIV protease inhibitor metabolized by cytochrome P450 monooxygenase.

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(54) Título: USO DE ATAZANAVIR ENTERAPIA DE VIH

(57) Resumen: Se divulga un método para reducir los niveles elevados en el plasma de LDL y/o de triglicéridos en pacientes infectados con VIH. En este método el atazanavir (BMS-232632) puede ser usado para tratar la infección del VIH en pacientes que exhiben niveles elevados de colesterol-LDL y/o triglicéridos, puede ser sustituido por un inhibidor agresivo de proteasa-VIH usado en tal terapia, o puede ser usado en combinación con un inhibidor de proteasa-VIH metabolizado por la citocromo P450 monooxigenasa.

USO DE ATAZANAVIR EN TERAPIA DE VIH

REFERENCIA A SOLICITUDES RELACIONADAS

Esta solicitud reivindica el beneficio del Número de Serie de Solicitud Provisional US número 60/316,745 entregada el 31 de Agosto de 2001.

CAMPO TECNICO

Esta invención se relaciona con métodos para reducir ciertos efectos metabólicos colaterales en los pacientes infectados con VIH, dichos efectos colaterales posiblemente como resultado de la administración de uno o más inhibidores de proteasa. Más en particular la invención se relaciona a la sustitución del inhibidor de proteasa VIH, atazanavir, por un inhibidor de proteasa VIH que ocasiona niveles elevados en la sangre de LDL y/o triglicéridos o la combinación de atazanavir con tales otros inhibidores de proteasa VIH.

FUNDAMENTO DE LA INVENCION

La terapia de combinación antirretroviral que incluye inhibidores de proteasa representa un avance significativo en la terapia de la infección del VIH. Los inhibidores de proteasa VIH pueden ser combinados con inhibidores del VIH de otras clases, por ejemplo inhibidores de transcriptasa reversa nucleósida o inhibidores de transcriptasa reversa no nucleósida, o usados con otros inhibidores de proteasa VIH, a veces también con inhibidores de la transcriptasa reversa nucleósida y/o inhibidores de transcriptasa reversa no nucleósida, en los denominados "cócteles".

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Se ha sugerido la combinación de inhibidores de proteasa para combatir la resistencia viral (ver por ejemplo U.S. 6.100.277). El inhibidor de proteasa ritonavir también ha sido divulgado como que mejora la farmacocinética de ciertos otros inhibidores de proteasa cuando se usan en combinación (ver por ejemplo U.S. 6.037.157).

Un número de inhibidores de proteasa VIH se encuentran en el mercado o bajo investigación clínica incluyendo al saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, atazanavir, tipranavir y lopanivir. El atazanavir (también denominado BMS-232632) se divulga en las patentes U.S. No 5.5984.911 y 6.166.004. La patente U.S. 6.087.383 divulga la sal cristalina de bisulfato de atazanavir. El atazanavir es un inhibidor azapeptídico actualmente en desarrollo y sometido a evaluación clínica. Tiene elevada potencia, un perfil de resistencia favorable y una dosis diaria proporciona apoyo de biodisponibilidad.

Se ha encontrado que la administración de la terapia del VIH que contiene inhibidores de proteasa VIH esta acompañada de ciertas anomalías metabólicas en un número significativo de pacientes, incluyendo una elevación en la concentración de lipoproteínas de baja densidad (LDL) y triglicéridos en el plasma. La elevación de los niveles de colesterol-LDL y triglicéridos en el plasma constituye un gran factor de riesgo para el desarrollo prematuro de aterosclerosis e hipertrigliceridemia, y también puede contribuir al desarrollo de enfermedades del corazón y pancreatitis. Cada inhibidor de proteasa difiere en sus efectos sobre los perfiles de lípidos en el suero, pero en general la experiencia presente es que, a la fecha, todos los inhibidores de este tipo han presentado éste riesgo metabólico. Parece ser que el ritonavir es el del mayor efecto, mientras que el indinavir, nelfinavir, amprenavir y saquinavir parecen tener efectos algo reducidos

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sobre los niveles de lípidos en el suero. Los niveles aumentados de colesterol-LDL y triglicéridos asociados con el uso de inhibidores de proteasa son de un interés creciente, particularmente cuando se emplean regímenes que contienen dos o más inhibidores de proteasa.

La frecuencia de hiperlipidemia en pacientes infectados de VIH que toman inhibidores de proteasa ha sido reportada como que varía en un rango desde 8% hasta tan alto como 66% (ver *Farmacoterapia*, 1999, 19:281-298)

Una solución sugerida al problema anterior ha sido la de administrar agentes antilipídicos a los pacientes con niveles elevados de lípidos en el plasma resultantes de la terapia con inhibidores de proteasa VIH. Sin embargo los agentes antilipídicos más comúnmente usados, los inhibidores de la coenzima-hidroximetilglutaril A (HMG-CoA) reductasa, o estatinas, son metabolizados por el sistema de la isoenzima citocromo P450. Por lo tanto, al menos con algunas estatinas tales como la simvastatina y la lovastatina, la eficacia antihiperlipidémica en los pacientes afectados con VIH que se encuentran en terapia de inhibidores de proteasa puede verse en riesgo con dosis estándar de estatina.

RESUMEN DE LA INVENCION

En un aspecto la presente invención proporciona un método para reducir los niveles elevados de colesterol-LDL y/o triglicéridos en el plasma en un paciente infectado con VIH sometido a terapia con uno o más inhibidores de proteasa VIH que resulta en tales niveles elevados de colesterol-LDL y/o triglicéridos, que comprende sustituir en tal terapia una cantidad de atazanavir inhibidora del VIH y reductora del colesterol-LDL y/o los triglicéridos por el inhibidor de proteasa VIH

agresivo. La reducción de la hiperlipidemia es similar a la lograda por el uso de una estatina, pero sin los efectos colaterales que se ven con el uso esta clase de agentes reductores de lípidos. En otro aspecto se proporciona un método para reducir los niveles elevados de colesterol-LDL y/o triglicéridos en el plasma en un paciente infectado con VIH sometido a una terapia de inhibidor de proteasa VIH el cual comprende administrar a dicho paciente una cantidad eficaz inhibidora de VIH de atazanavir en combinación con una cantidad inhibidora de VIH de al menos otro inhibidor de proteasa VIH el cual es metabolizado por la citocromo P450 monooxigenasa. En aun otro aspecto se proporciona un método para el tratamiento de la infección de VIH en un paciente que exhibe niveles elevados de colesterol-LDL y/o triglicéridos en el plasma que comprende administrar a dicho paciente una cantidad de atazanavir inhibidora del VIH.

DESCRIPCION DETALLADA DE LA INVENCION

La presente invención se basa en una observación inesperada que el atazanavir, contrario a otros inhibidores de proteasa VIH, no tiene un efecto significativo sobre los niveles de Colesterol-LDL y/o triglicéridos en el plasma cuando se administra en dosis inhibidoras normales.

En estudios clínicos llevados a acabo en 98 los pacientes VIH positivo que habían tomado atazanavir por un año, no se observaron incrementos en el colesterol-LDL o los triglicéridos en el plasma. Por lo tanto el atazanavir es particularmente útil en el tratamiento de pacientes VIH positivos que tienen niveles elevados de colesterol-LDL y/o triglicéridos en el plasma. Se puede usar como monoterapia o como parte de un "cóctel" el cual incluirla otras drogas antirretrovirales tales como inhibidores de transcriptaza reversa, inhibidores de transcriptaza reversa no

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nucleósida y otros inhibidores de proteasa VIH. Entonces en un aspecto, la presente invención proporciona un método para tratar la infección del VIH en un paciente que exhibe niveles elevados de colesterol-LDL y/o triglicéridos en el plasma que comprende administrar a dicho paciente una cantidad de atazanavir inhibidora del VIH.

El atazanavir es especialmente útil en el tratamiento de pacientes infectados con VIH que tienen niveles elevados de colesterol-LDL y/o triglicéridos en el plasma resultantes de una terapia antirretroviral con un inhibidor de proteasa VIH.

En un estudio aleatorio de Fase II se comparó la seguridad y la actividad anti-VIH de tres dosis, una vez por día, de atazanavir (200 mg, 400 mg y 500 mg) con 750 mg del inhibidor de proteasa nelfinavir, dosificado tres veces al día. Veintiún pacientes recibieron nelfinavir en combinación con stavudine y didanosine, mientras que el atazanavir fue administrado tanto como monoterapia (por dos semanas) y luego en combinación con stavudine y didanosine a 78 pacientes sin tratamiento previo (sin terapia de VIH previa) con cargas virales de VIH de > 2000 copias por mililitro (c/ml). Los pacientes en los brazos de atazanavir mostraron al menos reducciones comparables en la carga viral en comparación con los pacientes tratados con nelfinavir, pero no mostraron cambios en los niveles de lípidos mientras que tras cuatro semanas aquellos en el brazo de nelfinavir tenían un incremento en los niveles de colesterol total, colesterol-LDL y triglicéridos.

En otro estudio aleatorio de Fase II de tres brazos y de dos etapas se compararon la actividad antiviral y los efectos metabólicos del atazanavir a dos dosis diferentes (400 mg o 600 mg) con las del ritonavir, cada uno en combinación con saquinavir durante 48 semanas. Los inhibidores de proteasa fueron administrados en

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combinación con dos inhibidores de transcriptasa reversa nucleósida seleccionados de didanosina, stavudina, lamivudina o zidovudina. La selección de los inhibidores de transcriptasa reversa (usados en combinación como didanosina + stavudina, stavudina + lamivudina, didanosina + zidovudina o lamivudina + zidovudina) se basó en la sensibilidad fenotípica del paciente y el criterio del médico al momento de la administración. Los regímenes fueron de la siguiente forma:

atazanavir 400 mg QD + saquinavir 1200 mg QD + 2 inhibidores de transcriptasa reversa nucleósida.

atazanavir 600 mg QD + saquinavir 1200 mg QD + 2 inhibidores de transcriptasa reversa nucleósida.

atazanavir 400 mg QD + saquinavir 400 mg QD + 2 inhibidores de transcriptasa reversa nucleósida.

Los pacientes tenían experiencia de tratamiento antirretroviral con un historial de haber recibido por un mínimo de 24 semanas un régimen que contenía un inhibidor de proteasa o un inhibidor de transcriptasa reversa no nucleósida. La Etapa 1 fue aleatorizar aproximadamente 75 sujetos para evaluar la seguridad y la actividad antiviral de los regímenes. Siguiendo una evaluación de seguridad inicial de la Etapa I, se distribuyeron Aleatoriamente otros 300 pacientes adicionales en la Etapa II para evaluar la magnitud y la duración de la reducción del RNA VIH en el plasma desde la línea base hasta la semana 48. Se compararon los dos grupos de atazanavir con el ritonavir en términos del cambio promedio en el colesterol total desde la línea base en la semana 12. Los estimados de la diferencia para las

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comparaciones en parejas fueron – 49.1 para la pareja atazanavir 600 mg-ritonavir y – 28.7 para la pareja atazanavir 400 mg-ritonavir. El colesterol total no fue elevado en ninguno de los grupos con atazanavir. Los cambios en la mediana desde la línea base en la semana 12 fueron – 20 mg/dL para el atazanavir 600 mg y 5 mg/dL para el atazanavir 400 mg comparados con 37 mg/dL para el ritonavir. Los datos fraccionados del colesterol estuvieron disponibles en la línea base y en la semana 12 en aproximadamente ¼ de los pacientes. El colesterol-LDL no se elevó por encima de la línea base en ningún grupo de atazanavir.

Los dos grupos de atazanavir fueron comparados con el ritonavir en términos del cambio promedio en los triglicéridos desde la línea base en la semana 12. Los estimados de la diferencia para las comparaciones en parejas fueron – 135.9 para atazanavir 600-ritonavir y – 155.2 para atazanavir 400-ritonavir. Los cambios en la mediana desde la línea base en la semana 12 fueron - 5 mg/dL para atazanavir 600 mg y - 14 mg/dL para atazanavir 400 comparados con 102 mg/dL para el ritonavir. Los dos grupos mostraron una eficacia antiviral similar a través de la semana 12. Este estudio muestra que los pacientes con niveles elevados de colesterol-LDL y triglicéridos en el plasma pueden ser cambiados efectivamente a una terapia que contiene atazanavir para mantener la supresión viral mientras se reducen los niveles de colesterol-LDL y triglicéridos. Por lo tanto, el método de la presente invención proporciona una alternativa efectiva y segura a la intervención con estatina que puede resultar en riesgos adicionales de efectos colaterales e impactar de forma adversa otras medicaciones.

El atazanavir puede ser empleado solo o en combinación con una o más de otras sustancias farmacéuticamente activas que son activas contra retrovirus, especialmente el VIH. Tales otras sustancias pueden ser, por ejemplo, inhibidores

de la transcriptasa reversa como zidovudina, didanosina, stavudina, zalcitabina o lamivudina, inhibidores de la transcriptasa reversa no nucleósida como el efavirenz, u otros inhibidores de la proteasa VIH.

El atazanavir normalmente se obtiene como una basa orgánica débil y es comúnmente convertida para formulación farmacéutica en sales de adición ácida farmacéuticamente aceptables tales como aquellas descritas en la patente U.S. 6.166.004. Una forma muy preferida de sal para composiciones farmacéuticas es la sal de bisulfato descrita en la patente U.S. 6.087.383.

En el proceso de la presente invención, uno comienza con un paciente infectado de VIH que tiene niveles elevados de colesterol-LDL y triglicéridos en el plasma. En un aspecto de la invención, tal paciente ha sido o está siendo sometido a una terapia antirretroviral con uno o más inhibidores de proteasa VIH diferentes al atazanavir y exhibe niveles elevados de colesterol-LDL y/o triglicéridos en el plasma. Tales otros inhibidores de proteasa VIH pueden ser dados como monoterapia o como parte de una terapia antirretroviral la cual también incluye una o más de otras drogas antirretrovirales tales como inhibidores de transcriptasa reversa o inhibidores de transcriptasa reversa no nucleósida. Tales candidatos, aunque pueden exhibir supresión viral satisfactoria, pueden ser de riesgo aumentado para hiperlipidemia y eventos cardiovasculares prematuros.

El término "niveles elevados de colesterol-LDL y triglicéridos en el plasma" como se usa aquí está basado en los lineamientos de la práctica clínica del Programa Nacional de Educación del Colesterol (NCEP, por sus siglas en inglés) para la prevención y el manejo del colesterol en adultos. En la última edición de los

lineamientos del 2001, los niveles de colesterol-LDL > 130 mg/dL y de triglicéridos > 150 mg/dL en el plasma se consideran elevados o "altos". El proceso de la presente invención es particularmente útil para aquellos pacientes que tienen niveles de triglicéridos > 200 mg/dL en el plasma y para aquellos pacientes sin factores de riesgo o eventos cardiovasculares previos que tienen niveles de colesterol-LDL > 160 mg/dL. La definición de niveles "elevados" de colesterol-LDL y triglicéridos puede, por supuesto, cambiar en el futuro a medida que la NCEP continúa evaluando factores de riesgo de ataques cardíacos. Se intenta, entonces, que el término "niveles elevados de colesterol-LDL y triglicéridos" se emplee en consistencia con los lineamientos actuales de la NCEP.

En uno de sus aspectos, la presente invención involucra discontinuar el inhibidor de proteasa VIH agresivo (la droga responsable de los niveles elevados de colesterol-LDL y triglicéridos en el plasma) del régimen antes mencionado y por lo tanto sustituyendo una cantidad de atazanavir la cual es efectiva para inhibir el VIH y en reducir los niveles de colesterol-LDL y/o triglicéridos en el plasma.

La dosis a usar de atazanavir depende de factores tales como el peso corporal, la edad y la condición individual del paciente a ser tratado y del modo de administración. En general las dosis de entre 3 mg a aproximadamente 1.6 gramos por persona por día, divididas en 1 a 3 dosis individuales, son apropiadas. Una dosis especialmente preferida para pacientes adultos es de 50 – 800, más preferiblemente de 400 – 600 y más preferiblemente aun 400 mg dados una vez al día.

Las composiciones farmacéuticas de atazanavir que se pueden emplear en el proceso de la presente invención son aquellas descritas, por ejemplo, en las

patentes U.S. 6.166.004 y 6.087.383. Formas apropiadas de administración oral incluyen cápsulas, tabletas y polvos para suspensión oral.

También se ha encontrado que el atazanavir es un inhibidor de la citocromo 450P monooxigenasa y que puede mejorar la farmacocinética de las drogas metabolizadas por esta enzima, incluyendo particularmente otros inhibidores de proteasa VIH tales como el saquinavir, indinavir, nelfinavir, amprenavir, tipanavir y lopinavir. Por lo tanto, actúa en una forma similar al ritonavir descrito en la patentes U.S. 6.037.157 para incrementar los niveles en la sangre del inhibidor de proteasa VIH administrado de forma conjunta. Una diferencia notable del ritonavir es que el atazanavir se emplea en terapia de combinación con otros inhibidores de proteasa VIH a su nivel de dosis terapéutico en lugar del nivel de dosis subterapéutico usado con el ritonavir. Debido a su nivel potenciador sobre otros inhibidores de proteasa VIH los cuales son metabolizado por la citocromo P450 monooxigenasa, el uso de atazanavir en concomitancia con otros inhibidores de proteasa VIH permite el uso de dosis reducidas de tales otros inhibidores de proteasa VIH mientras se mantiene el mismo nivel de supresión viral. Por ejemplo, en el estudio de Fase II anteriormente descrito la dosis de saquinavir pudo ser ajustada de su dosis recomendada de 1200 mg 3 veces al día a 1200 mg una vez al día cuando se combina con atazanavir. El atazanavir puede ser usado en combinación con otros inhibidores de proteasa VIH para reducir los niveles de colesterol-LDL y triglicéridos en paciente con SIDA sometidos a una terapia de inhibidores de proteasa mientras mantiene el nivel deseado de supresión viral.

La dosis apropiada del inhibidor de proteasa VIH que se va a combinar con el atazanavir se puede determinar por el siguiente método el cual fue usado para la combinación atazanavir/saquinavir:

El atazanavir es un inhibidor moderado de la enzima citocromo P450 comparable con el nelfinavir y el indinavir, con un K_i de 2.4 μ M. Los dos últimos compuestos incrementaron la exposición del saquinavir (dosificado a 1200 mg tres veces al día (TID, por sus siglas en inglés)) en un 392 y 364% respectivamente, en estado estable. Se completó un estudio farmacológico de dosis múltiple para evaluar si se podía esperar un incremento similar de la combinación de atazanavir y saquinavir. Este estudio demostró un incremento de más de 3 veces en la exposición, debido a una combinación con atazanavir, soportando una dosis de saquinavir de 1200 mg una vez al día, fue equivalente al régimen actualmente comercializado de 1200 mg de saquinavir TID. Usando una dosis constante de atazanavir se estudió el rango de las dosis de saquinavir para apuntar a la exposición de saquinavir (AUC (área bajo la curva, por sus siglas en inglés) y CMIN (concentración mínima, por sus siglas en inglés)) similares a aquellas de la literatura. De manera similar, se pueden calcular las dosis apropiadas de otros inhibidores de proteasa VIH a ser usados en combinación con el atazanavir.

Entonces, en otro aspecto la presente invención proporciona un método para reducir los niveles de colesterol-LDL y/o triglicéridos en el plasma en un paciente infectado con VIH sometido a una terapia inhibidora de proteasa VIH el cual comprende administrar a dicho paciente una cantidad inhibidora de VIH efectiva de atazanavir en combinación con una cantidad inhibidora de VIH de al menos un inhibidor de proteasa VIH metabolizado por la citocromo P450 monooxigenasa.

La presente invención también proporciona composiciones farmacéuticas que comprenden una cantidad efectiva de atazanavir inhibidora del VIH y una cantidad efectiva inhibidora del VIH de al menos otro inhibidor de proteasa VIH el cual es metabolizado por la citocromo P450 monooxigenasa. Composiciones en forma de

cápsulas, tabletas, aspersores nasales, soluciones, polvos, gránulos, emulsiones, jarabes, supositorios, liposomas, suspensiones, etc, tales como las divulgadas en la patente U.S. 6.166.004 son apropiadas para la presente invención.

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REVINDICACIONES

Lo que se reivindica es:

- 1. Un método para reducir los niveles elevados de colesterol-LDL y/o triglicéridos en el plasma en un paciente infectado de VIH que resultan de la terapia con uno o más inhibidores de proteasa VIH, que comprende sustituir una cantidad de atazanavir inhibidora de VIH y reductora de LDL y/o triglicéridos por el inhibidor de proteasa VIH agresivo usado en tal terapia.**
- 2. Un método para reducir los niveles elevados de colesterol-LDL y/o triglicéridos en el plasma en un paciente infectado de VIH sometido a una terapia de proteasa VIH el cual comprende administrar a dicho paciente una cantidad efectiva de atazanavir inhibidora de VIH en combinación con una cantidad inhibidora del VIH de al menos un inhibidor de proteasa VIH metabolizado por la citocromo P450 monooxigenasa.**
- 3. El método de la reivindicación 2 en dónde el atazanavir es administrado en combinación con un inhibidor de proteasa VIH seleccionado de saquinavir, indinavir, amprenavir, nelfinavir, tipanavir o lopinavir.**
- 4. El método de la reivindicación 3 en dónde el atazanavir es administrado en combinación con saquinavir.**
- 5. Un método para tratar la infección de VIH en un paciente que exhibe niveles elevados de colesterol-LDL y/o triglicéridos en el plasma que comprende administrar a dicho paciente una cantidad inhibidora de VIH de atazanavir.**

AUG 04 2003

PATENT COOPERATION TREATY

Docketed Item _____

Due Date _____

Attorney _____

PCT

(WV)

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYTo:
DAVID M. MORSE
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
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21 August 2002 (21.08.2002)

31 August 2001 (31.08.2001)

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.

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CT-2679		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US02/26675	International filing date (day/month/year) 21 August 2002 (21.08.2002)	Priority date (day/month/year) 31 August 2001 (31.08.2001)	
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/7072, 551 and US Cl.: 514/50, 220			
Applicant BRISTOL-MYERS SQUIBB COMPANY			
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. 2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. ☐ 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). These annexes consist of a total of <u> </u> sheets.			
3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) 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			
Date of submission of the demand 14 March 2003 (14.03.2003)		Date of completion of this report 02 July 2003 (02.07.2003)	
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230		Authorized officer Zohreh Fay  Telephone No. 703-308-1235	

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/26675

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I. Basis of the report

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

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-9 _____ as originally filed
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.
- ☒ the claims:
pages 10 _____, 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.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US02/26675

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 2

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require international preliminary examination (specify):

☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. 2 are so unclear that no meaningful opinion could be formed (specify):

Present claim 2 relates to compounds defined by reference to a desirable characteristic or property, namely "HIV protease inhibitors". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only very limited number of such compounds. Moreover, the claimed combination, namely "one or more HIV protease inhibitors" in combination with zalcitabine covers numerous possible combinations. In the present case, the claims so lack support, and the applications so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again this search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in the examples specified in claim 3.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/26673

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 1, 3-5	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1, 3-5	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1, 3-5	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Document D1 (Database Medline on STN, No. 2003007811, SANNE et al., Journal OF ACQUIRED IMMUNE DEFICIENCY SYNDROME, 2003, 32(1) 18-29) discloses the mean percent change from baseline in fasting LDL cholesterol is significantly less in the abacavir treated patient. In addition, Document D1 discloses that abacavir is not associated with clinically relevant increases in total cholesterol, fasting LDL cholesterol, or fasting triglycerides. Document D1 defines the general state of the art, but it is not considered to be of particular relevance.

Document D2 (Database CAPLUS on STN, No. 2202:891974, DE CLERQ, E., Medicinal Research Reviews, 2002, 22(6), 532-565) relates to the use of various new NRTIs, NNRTIs, and PIs including abacavir as an anti-HIV agents. Document D2 is not considered to be of particular relevance.

Claims 1, 3-5 do meet Novelty and Inventive Step criteria under PCT Article 33(2)-(3) because none of the prior art teaches or suggests the use of abacavir alone or combination with an HIV protease inhibitor for reducing elevated plasma LDL and/or triglyceride levels in an HIV-infected patient.

Claims 1, 3-5 do meet Industrial Applicability criteria under PCT Article 33(4) since the claiming subject matter relates the medical use.

NEW CITATIONS

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**TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES**

PCT

**INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 PCT)**

No. de Expediente del Solicitante o Apoderado CT-2679	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del informe de examen preliminar internacional (Formulario PCT/IPEA/416)		
No. Solicitud Internacional PCT/US02/26675	<table style="width: 100%;"> <tr> <td style="width: 50%;"> Fecha Internacional de Presentación (día/mes/año) 21 de Agosto de 2002 (21.08.2002) </td> <td style="width: 50%;"> Fecha de Prioridad (día/mes/año) 31 de Agosto de 2001 (31.08.2001) </td> </tr> </table>	Fecha Internacional de Presentación (día/mes/año) 21 de Agosto de 2002 (21.08.2002)	Fecha de Prioridad (día/mes/año) 31 de Agosto de 2001 (31.08.2001)
Fecha Internacional de Presentación (día/mes/año) 21 de Agosto de 2002 (21.08.2002)	Fecha de Prioridad (día/mes/año) 31 de Agosto de 2001 (31.08.2001)		
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC IPC(7): A61K 31/7072, 551 y US Cl.: 514/450,220			
Solicitante BRISTOL-MYERS SQUIBB COMPANY			

1.	Este informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 38.																								
2.	Este INFORME comprende un total de <u>4</u> hojas, inclusive esta portada ☐ Además se adjuntan ANEXOS al informe; en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos, que se modificaron y que sirven de base a este informe, y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70.16 y Sección 607 de las Instrucciones administrativas al PCT). Estos anexos comprenden en total de <u>0</u> hojas.																								
3.	Este informe contiene datos con respecto a los siguientes puntos: <table style="width: 100%; margin-top: 10px;"> <tr> <td style="width: 5%;">I</td> <td style="width: 5%;">☒</td> <td>Base del Informe</td> </tr> <tr> <td>II</td> <td>☐</td> <td>Prioridad</td> </tr> <tr> <td>III</td> <td>☐</td> <td>Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial</td> </tr> <tr> <td>IV</td> <td>☐</td> <td>Uniformidad deficiente de la invención</td> </tr> <tr> <td>V</td> <td>☒</td> <td>Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración</td> </tr> <tr> <td>VI</td> <td>☐</td> <td>Ciertos documentos enumerados</td> </tr> <tr> <td>VII</td> <td>☐</td> <td>Ciertas deficiencias del registro internacional</td> </tr> <tr> <td>VIII</td> <td>☐</td> <td>Ciertas observaciones relacionadas con la solicitud internacional</td> </tr> </table>	I	☒	Base del Informe	II	☐	Prioridad	III	☐	Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial	IV	☐	Uniformidad deficiente de la invención	V	☒	Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración	VI	☐	Ciertos documentos enumerados	VII	☐	Ciertas deficiencias del registro internacional	VIII	☐	Ciertas observaciones relacionadas con la solicitud internacional
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VI	☐	Ciertos documentos enumerados																							
VII	☐	Ciertas deficiencias del registro internacional																							
VIII	☐	Ciertas observaciones relacionadas con la solicitud internacional																							

Fecha de presentación de la petición 14 de Marzo de 2003 (14.03.2003)	Fecha de la preparación de este informe 5 de Julio de 2003 (02.07.2003)
Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional (IPEA/US) Mail Stop PCT, Attn: IPEA/US Comisionado de Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimil No. (703)305-3230	Empleado Autorizado Zohrek Fay Telefono 703 308-1235

Formulario PCT/IPEA/409 (hoja de portada)(Julio de 1998)

TRATADO DE COOPERACIÓN DE PATENTES

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Remitente:

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

PCT

NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE DEL EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 PCT)

A:
DAVID M. MORSE
BRYSTOL-MYERS SQUIBB COMPANY
APARTADO POSTAL 4000
PRINCETON, NJ 08543-4000

Fecha de envío
(Día/Mes/Año)

31 DE JULIO DE 2003

No. de Expediente del Solicitante o Apoderado

CT-2679

COMUNICACIÓN IMPORTANTE

No. de Solicitud Internacional

PCT/US 02/26675

Fecha Internacional de Presentación
(día/mes/año)

21 de Agosto de 2002
(21.08.2002)

Fecha de Prioridad (día/mes/año)

31 de Agosto de 2001
(31.08.2001)

Solicitante

BRISTOL-MYERS SQUIBB COMPANY

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional, elaborado para la solicitud internacional, en caso dado con los anexos correspondientes.

2. Una copia del informe, en caso dado con los anexos correspondientes, se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.

3. A solicitud de una oficina seleccionada, la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.

4. RECORDATORIO

Para ingresar en la fase nacional el solicitante, dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después), tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301).

Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional, entonces esta traducción tiene que incluir traducciones de todos los anexos al informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

Nombre y dirección postal de la Oficina Encargada del
Examen Preliminar Internacional (IPEA/US)

Mall Srop PCT, Attn: IPEA/US
Comisionado de Patentes
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimil No. (703)305-3230

Formulario PCT/IPEA/416 (Julio 1992)

Empleado Autorizado

Zohreh Fay

Teléfono No. 703-308-1235

I. Bases para este reporte.

1. Respecto a los elementos de la solicitud internacional:*

- ☒ la solicitud internacional como se entregó originalmente
- ☒ la descripción:
- páginas 1-9 como se entregaron originalmente
- páginas NINGUNA como se entregaron con la demanda
- páginas NINGUNA como se entregaron con la carta de _____
- ☒ las reivindicaciones:
- páginas 10 como se entregaron originalmente
- páginas NINGUNA como se corrigieron (junto con cualquier declaración) bajo el Artículo 19
- páginas NINGUNA como se entregaron con la demanda
- páginas NINGUNA como se entregaron con la carta de _____
- ☒ los dibujos
- páginas NINGUNA como se entregaron originalmente
- páginas NINGUNA como se entregaron con la demanda
- páginas NINGUNA como se entregaron con la carta de _____
- ☐ la lista de la descripción
- páginas NINGUNA como se entregaron originalmente
- páginas NINGUNA como se entregaron con la demanda
- páginas NINGUNA como se entregaron con la carta de _____

2. Respecto al idioma, todos los elementos anteriormente marcados estaban disponibles o fueron suministrados a esta oficina en el idioma en el que se entregó la solicitud internacional, a menos que se diga lo contrario en este punto. Estos elementos estaban disponibles o fueron entregados a esta oficina en el siguiente idioma _____ los cuales son

- ☐ El idioma de la traducción entregada para propósitos de la búsqueda internacional (Regla 23.1 (b)).
- ☐ El idioma de publicación de la solicitud internacional (bajo la Regla 48.3 (b)).
- ☐ El idioma de la traducción entregada para propósitos del examen preliminar internacional (bajo las Reglas 55.2 y/o 55.3)

3. respecto a cualquier secuencia de nucleótido y/o aminoácidos divulgados en esta solicitud internacional, el examen preliminar internacional se realizó sobre la base de la secuencia:

- ☐ contenida en la solicitud en forma impresa
- ☐ entregada junto con la solicitud internacional en una forma legible en un computador
- ☐ suministrada subsiguientemente a esta oficina de forma escrita
- ☐ suministrada subsiguientemente a esta oficina en forma legible en un computador
- ☐ la declaración que la secuencia escrita suministrada no va más allá de lo divulgado en la solicitud internacional como se entregó ha sido suministrada
- ☐ La declaración que la información registrada en la forma legible a computador es idéntica a la secuencia escrita ha sido suministrada.

4. ☒ Las correcciones han resultado en la cancelación de:

- ☒ la descripción, páginas NINGUNA
- ☒ las reivindicaciones, Nos. NINGUNA
- ☒ los dibujos, hojas/figuras NINGUNA

5. ☐ Este Informe ha sido admitido como si (algunas de) las enmendaduras no hubieran sido hechas, ya que se considera que estas van más allá de la divulgación preliminar, como se indica el Apartado Suplementario (Regla 70.2 (c)). **

* Las hojas de reemplazo que han sido suministradas a la Oficina receptora en respuesta a una invitación bajo el Artículo 14 se mencionan en este Informe como "entregadas originalmente" y no se anexan a este Informe ya que no contienen enmendaduras (Reglas 70.16 y 70.17)

** Cualquier hoja de reemplazo que contiene tales enmiendas debe mencionarse bajo el asunto 1 de este informe.

INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

No. de Solicitud Internacional
PCT/US02/26675

III. Sin establecimiento de una opinión con respecto a la novedad, el nivel inventivo o la aplicabilidad Industrial.

1. La pregunta de si la invención reivindicada parece ser nueva, involucra un nivel inventivo o es industrialmente aplicable no ha sido y no será examinada con respecto a:

☐ La totalidad de la solicitud internacional

☒ La(s) reivindicación(es) No. 2

Porque:

☐ Dicha solicitud internacional, o dichas reivindicaciones No. ____ se relacionan a la siguiente materia la cual no requiere del examen preliminar (*especifique*)

☒ La descripción, las reivindicaciones o los dibujos (*indique a continuación los elementos particulares*) o dichas reivindicaciones No. 2 son tan poco claras que no se puede formar una opinión significativa (*especifique*):

La reivindicación 2 actual se relaciona con compuestos definidos por referencia a una característica o propiedad deseable, a saber "inhibidores de proteasa VIH". Las reivindicaciones cubren todos los compuestos que tienen esta característica o propiedad, mientras que la solicitud proporciona sustento dentro del significado del artículo 6 del PCT y/o divulgación dentro del artículo 5 del PCT solo para un número limitado de tales compuestos. Más aun, la combinación reivindicada, a saber "uno o más inhibidores de proteasa VIH" en combinación con atazanavir cubre numerosas combinaciones posibles. En el caso presente, las reivindicaciones carecen tanto de soporte, y la solicitud carece tanto de divulgación, que una búsqueda significativa de todo el espectro reivindicado es imposible. Independiente de este razonamiento, las reivindicaciones también carecen de claridad (artículo 6 del PCT). Se hizo un intento para definir el compuesto por referencia a un resultado que debe ser logrado. Otra vez esta búsqueda sobre la totalidad del espectro reivindicado es imposible. Consecuentemente, la búsqueda se ha realizado para aquellas partes de las reivindicaciones que parecen ser claras, con sustento y divulgación, a saber aquellas partes relacionadas con los compuestos mencionados específicamente en los ejemplos especificados en la reivindicación 3.

☐ Las reivindicaciones, o dichas reivindicaciones No. ____ están tan inadecuadamente sustentadas por la descripción que no puede formar una opinión significativa

☐ No se ha establecido un Informe de búsqueda internacional para dichas reivindicaciones No. ____.

2. No se puede llevar a cabo un examen preliminar internacional debido a la falla de la secuencia de nucleótidos y/o aminoácidos de cumplir con el estándar proporcionado en el anexo C de las Instrucciones Administrativas:

☐ No se ha entregado la forma escrita o no cumple con el estándar.

☐ No se ha entregado el forma legible a computador o no cumple con el estándar.

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INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

No de Solicitud Internacional
PCT/US02/26675

V. Declaración concluyente de acuerdo a la Regla 68.2 (a)(ii) con relación a la novedad, el nivel inventivo o la aplicabilidad industrial; citas y explicaciones que soportan tal declaración

1. DECLARACIÓN

Novedad (N)	Reivindicaciones 1, 3-5	Si
	Reivindicaciones NINGUNA	No
Nivel Inventivo (IS)	Reivindicaciones 1, 3-5	Si
	Reivindicaciones NINGUNA	No
Aplicabilidad Industrial (IA)	Reivindicaciones 1, 3-5	Si
	Reivindicaciones NINGUNA	No

2. CITAS Y EXPLICACIONES

El documento D1 (Base de datos Medline en STN No. 2003007811, Sanne y colaboradores, Publicación de EL SINDROME DE INMUNODEFICIENCIA ADQUIRIDA, 2003, 32(1) 18-29) divulga que el porcentaje promedio de cambio desde la línea base en el aseguramiento del colesterol LDL es significativamente menor en el paciente tratado con atazanavir. Adicionalmente el documento D1 divulga que el atazanavir no está asociado con incrementos clínicamente relevantes en el colesterol total, el aseguramiento del colesterol LDL o el aseguramiento de los triglicéridos. El Documento D1 define el estado general del arte, pero no se considera de relevancia particular.

El Documento D2 (Base de datos CAPLUS en STN, No. 2202:891974, DE CLERCQ, E., Informes de Investigación Medicinal, 2002, 22(6), 535-565) se relaciona con el uso de varios NRTIS, NNRTIS y PI's nuevos incluyendo el atazanavir como agentes anti-VIH. El Documento D2 no es considerado de relevancia particular.

Las reivindicaciones 1, 3-5 si cumplen con el criterio de Novedad y Nivel Inventivo bajo el artículo 33(2)-(3) debido a que nada en el arte previo enseña o sugiere el uso de atazanavir solo o combinado con un inhibidor de proteasa VIH para reducir los niveles elevados de LDL y/o triglicéridos en un paciente infectado de VIH.

Las reivindicaciones 1, 3-5 cumplen con el criterio de Aplicabilidad Industrial bajo el artículo 33(4) debido a que la materia reivindicada se relaciona al uso médico.

____NUEVAS CITAS____

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H**USE OF ATAZANAVIR IN HIV THERAPY****REFERENCE TO RELATED APPLICATIONS**

- 5 This application claims the benefit of U.S. Provisional Application Serial Number 60/316,745 filed August 31, 2001.

TECHNICAL FIELD

- 10 This invention relates to methods for reducing certain metabolic side effects in HIV-infected patients, said side effects possibly resulting from the administration of one or more HIV protease inhibitors. More particularly, the invention relates to the substitution of the HIV protease inhibitor, atazanavir, for an HIV protease inhibitor causing elevated blood LDL and/or triglyceride levels or the combination of
15 atazanavir with such other HIV protease inhibitor.

BACKGROUND OF THE INVENTION

- Combination antiretroviral therapy that includes protease inhibitors represents
20 a significant advance in the therapy of HIV infection. HIV protease inhibitors may be combined with HIV inhibitors of other classes, e.g. nucleoside reverse transcriptase inhibitors or non-nucleoside reverse transcriptase inhibitors, or used with other HIV protease inhibitors, often also with nucleoside reverse transcriptase inhibitors and/or non-nucleoside reverse transcriptase inhibitors, in so-called "cocktails".
- 25 Combinations of protease inhibitors have been suggested to combat viral resistance (see, for example, U.S. 6,100,277). The protease inhibitor, ritonavir, has also been disclosed as improving the pharmacokinetics of certain other protease inhibitors when used in combination (see, for example, U.S. 6,037,157).
- 30 A number of HIV protease inhibitors are on the market or under clinical investigation including saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, atazanavir, tipranavir, and lopinavir. Atazanavir (also referred to as BMS-232632) is disclosed in U.S. Patents 5,849,911 and 6,166,004. U.S. Patent 6,087,383 discloses

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the crystalline bisulfate salt of atazanavir. Atazanavir is an azapeptide inhibitor currently in development and undergoing clinical evaluation. It has high potency, a favorable resistance profile, and bioavailability supportive of once-daily oral dosing.

5 Administration of HIV therapy containing HIV protease inhibitors has been found to be accompanied by certain metabolic abnormalities in a significant number of patients, including an elevation in plasma concentrations of low-density lipoproteins (LDL) and triglycerides. Elevation in plasma levels of LDL-cholesterol and triglycerides constitutes a major risk factor for the premature development of
10 atherosclerosis and hypertriglyceridemia, and may also contribute to the development of heart disease and pancreatitis. Individual protease inhibitors differ in their effects on serum lipid profiles, but in general, the current experience is that, to date, all such inhibitors have exhibited this metabolic liability. Ritonavir seems to have the greatest effect, while indinavir, nelfinavir, amprenavir, and saquinavir
15 appear to have somewhat reduced effects on serum lipid levels. The increased LDL-cholesterol and triglyceride levels associated with protease inhibitor use are of growing concern, particularly when regimens containing two or more protease inhibitors are employed.

20 The frequency of hyperlipidemia in HIV-infected patients taking protease inhibitors has been reported to range from 8% to as high as 66% (see *Pharmacotherapy*, 1999, 19:281-298).

One suggested solution to the above problem has been to administer
25 antilipidemic agents to patients having elevated plasma lipid levels resulting from HIV protease inhibitor therapy. However, the most commonly used antilipidemic agents, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, are metabolized by the cytochrome P450 isoenzyme system. Thus, at least with some statins such as simvastatin and lovastatin, antihyperlipidemic efficacy in
30 HIV-infected patients on protease inhibitor therapy may be compromised at standard statin doses.

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SUMMARY OF THE INVENTION

In one aspect, there is provided by the present invention a method for reducing elevated plasma LDL-cholesterol and/or triglyceride levels in an HIV-
5 infected patient undergoing therapy with one or more HIV protease inhibitors resulting in such elevated LDL-cholesterol and/or triglyceride levels, comprising substituting in such therapy an HIV-inhibiting and LDL-cholesterol and/or triglyceride reducing amount of atazanavir for the offending HIV protease inhibitor. The reduction in hyperlipidemia is similar to that achieved by use of a statin, but
10 without the side effects seen with this class of lipid-lowering agents. In another aspect, there is provided a method for reducing elevated plasma LDL-cholesterol and/or triglyceride levels in an HIV-infected patient undergoing HIV protease inhibitor therapy which comprises administering to said patient an effective HIV-inhibiting amount of atazanavir in combination with an HIV-inhibiting amount of at
15 least one other HIV protease inhibitor which is metabolized by cytochrome P450 monooxygenase. In yet another aspect, there is provided a method for treating HIV infection in a patient exhibiting elevated plasma LDL-cholesterol and/or triglyceride levels comprising administering to said patient an HIV-inhibiting amount of atazanavir.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the unexpected observation that atazanavir, unlike other HIV protease inhibitors, has no significant effect on plasma LDL-
25 cholesterol and triglyceride levels when administered in normal HIV-inhibiting dosages.

In clinical studies carried out on 98 HIV-positive patients who have taken atazanavir for one year, no increases in plasma LDL-cholesterol or triglycerides were
30 observed. Thus, atazanavir is particularly useful in the treatment of HIV-positive patients who have elevated plasma LDL-cholesterol and/or triglyceride levels. It can be used as monotherapy or as part of a "cocktail" which would include other antiretroviral drugs such as reverse transcriptase inhibitors, non-nucleoside reverse

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transcriptase inhibitors, and other HIV protease inhibitors. In one aspect, then, the present invention provides a method for treating HIV infection in a patient exhibiting elevated plasma LDL-cholesterol and/or triglyceride levels comprising administering to said patient an HIV-inhibiting amount of atazanavir.

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Atazanavir is especially useful in the treatment of HIV-infected patients who have elevated plasma LDL-cholesterol and/or triglyceride levels resulting from antiretroviral therapy with an HIV protease inhibitor.

10 In a Phase II randomized study, the safety and anti-HIV activity of three once daily doses of atazanavir (200 mg, 400 mg and 500 mg) was compared with 750 mg of the protease inhibitor, nelfinavir dosed three times daily. Twenty-one patients received nelfinavir in combination with stavudine and didanosine, while atazanavir was administered both as monotherapy (for two weeks) and then in combination with
15 stavudine and didanosine to 78 treatment-naïve (no prior anti-HIV therapy) patients with HIV viral loads >2000 copies per milliliter (c/mL). Patients in the atazanavir arms showed at least comparable reductions in viral load compared to the nelfinavir-treated patients, but displayed no changes in lipid levels, while after four weeks, those in the nelfinavir arm had an increase in total cholesterol, LDL-cholesterol and
20 triglyceride levels.

In another two-stage, randomized three-arm Phase II study, the antiviral activity and metabolic effects of atazanavir at two different doses (400 mg or 600 mg) was compared to ritonavir, each in combination with saquinavir over 48 weeks.
25 The protease inhibitors were administered in combination with two nucleoside reverse transcriptase inhibitors selected from didanosine, stavudine, lamivudine or zidovudine. The selection of reverse transcriptase inhibitors (used in combination as didanosine + stavudine, stavudine + lamivudine, didanosine + zidovudine, or lamivudine + zidovudine) was based on the patient's phenotypic sensitivity and the
30 physician's choice at the time of administration. The regimens were as follows:

atazanavir 400 mg QD + saquinavir 1200 mg QD + 2 nucleoside reverse transcriptase inhibitors

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atazanavir 600 mg QD + saquinavir 1200 mg QD + 2 nucleoside reverse transcriptase inhibitors

5 ritonavir 400 mg BID + saquinavir 400 mg BID + 2 nucleoside reverse transcriptase inhibitors

Patients were anti-retroviral-experienced with a treatment history of receiving a minimum of 24 weeks of a protease inhibitor-containing or non-nucleoside reverse transcriptase inhibitor-containing combination regimen. Stage 1 was to randomize approximately 75 subjects to assess the safety and antiviral activity of the regimens. Following an initial safety assessment of Stage I, an additional 300 patients were randomized into Stage II to assess the magnitude and duration of reduction of plasma HIV RNA from baseline through week 48. The two atazanavir groups were compared to ritonavir in terms of the mean change in total cholesterol from baseline at week 12. The difference estimates for the pairwise comparisons were -49.1 for the atazanavir 600 mg -ritonavir pair and -28.7 for the atazanavir 400 mg-ritonavir pair. Total cholesterol was not elevated on either of the atazanavir groups. The median changes from baseline at week 12 were -20 mg/dL for atazanavir 600 mg and 5 mg/dL for atazanavir 400 compared to 37 mg/dL for ritonavir. Fractionated cholesterol data were available at baseline and week 12 on approximately 1/2 of the patients. LDL-cholesterol was not elevated over baseline on any atazanavir group.

The two atazanavir groups were compared to ritonavir in terms of the mean change in triglycerides from baseline at week 12. The difference estimates for the pairwise comparisons were -135.9 for atazanavir 600-ritonavir and -155.2 for atazanavir 400 mg-ritonavir. The median changes from baseline at week 12 were 5 mg/dL for atazanavir 600 mg and -14 mg/dL for atazanavir 400 mg compared to 102 mg/dL for ritonavir. The two groups showed similar antiviral efficacy through week 12. This study shows that patients with elevated plasma LDL-cholesterol and triglycerides can be effectively switched to an atazanavir-containing therapy to maintain viral suppression while reducing LDL-cholesterol and triglyceride levels. Thus, the method of the present invention provides an effective and safe alternative to

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statin intervention that can result in additional side effect risks and adversely impact other medications.

Atazanavir can be used alone or in combination with one or more other
5 pharmaceutically active substances that are active against retroviruses, especially HIV. Such other substances may be, for example, inhibitors of reverse transcriptase, e.g. zidovudine, didanosine, stavudine, zalcitabine, or lamivudine, non-nucleoside reverse transcriptase inhibitors such as efavirenz, or other HIV protease inhibitors.

10 Atazanavir is normally obtained as a weak organic base and is commonly converted for pharmaceutical formulation into pharmaceutically acceptable acid addition salts such as those described in U.S. Patent 6,166,004. A most preferred salt form for pharmaceutical compositions is the bisulfate salt described in U.S. Patent 6,087,383.

15 In the process of the present invention, one starts with an HIV-infected patient who has elevated plasma LDL-cholesterol and/or triglyceride levels. In one aspect of the invention, such patient has been or is undergoing antiretroviral therapy with one or more HIV protease inhibitors other than atazanavir and exhibits elevated plasma
20 LDL-cholesterol and/or triglyceride levels. Such other HIV protease inhibitor(s) may be given as monotherapy or as part of an antiretroviral therapy which also includes one or more other antiretroviral drugs such as reverse transcriptase inhibitors or non-nucleoside reverse transcriptase inhibitors. Such candidates, although they may exhibit satisfactory viral suppression, may be of increased risk for hyperlipidemia and
25 premature cardiovascular events.

The term "elevated plasma LDL-cholesterol and triglyceride levels" as used herein is based on the National Cholesterol Education Program (NCEP) clinical practice guidelines for the prevention and management of high cholesterol in adults.
30 In the latest guidelines issued in 2001, plasma levels of >130 mg/dL of LDL-cholesterol and >150 mg/dL of triglycerides are considered elevated or "high". The process of the present invention is particularly useful for those patients having plasma triglyceride levels of >200 mg/dL and for those patients with no risk factors

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or previous cardiovascular events having LDL-cholesterol levels of >160 mg/dL. The definition of "elevated" LDL-cholesterol and triglyceride levels may, of course, change in the future as the NCEP continues to evaluate heart attack risk factors. It is intended, then, that the term "elevated LDL-cholesterol and triglyceride levels" as
5 used will be consistent with current NCEP guidelines.

In one of its aspects, the present invention involves discontinuing the offending (the drug responsible for the elevated plasma LDL-cholesterol and/or triglyceride levels) HIV protease inhibitor from the above regimen and substituting
10 therefore an amount of atazanavir which is effective to inhibit HIV and to reduce plasma LDL-cholesterol and/or triglyceride levels.

The dose of atazanavir to be employed depends on such factors as the body weight, age and individual condition of the patient to be treated and the mode of
15 administration. In general dosages of from about 3 mg to approximately 1.6 grams per person per day, divided into 1 to 3 single doses, are suitable. An especially preferred dosage for adult patients is 50-800, more preferably 400-600 and most preferably 400 mg given once daily.

20 The pharmaceutical compositions of atazanavir that may be used in the process of the present invention are those described, for example, in U.S. Patents 6,166,004 and 6,087,383. Suitable forms for oral administration include capsules, tablets and powders for oral suspension.

25 Atazanavir has also been found to be an inhibitor of cytochrome P450 monooxygenase and can improve the pharmacokinetics of drugs metabolized by this enzyme, including particularly other HIV protease inhibitors such as saquinavir, indinavir, nelfinavir, amprenavir, tipranavir and lopinavir. Thus, it acts in a similar way to ritonavir described in U.S. Patent 6,037,157 to increase blood levels of the co-
30 administered HIV protease inhibitor. One notable difference from ritonavir is that atazanavir is employed in combination therapy with other HIV protease inhibitors at its normal therapeutic dose level instead of the sub-therapeutic dose levels used with ritonavir. Because of its potentiating effect on other HIV protease inhibitors which

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are metabolized by cytochrome P450 monooxygenase, use of atazanavir concomitantly with such other HIV protease inhibitors allows reduced dosages of such other HIV protease inhibitors to be used while maintaining the same degree of viral suppression. For example in the Phase II study described above, the dosage of saquinavir could be adjusted from its recommended dosage of 1200 mg 3 times daily to 1200 mg once daily when combined with atazanavir. Atazanavir can be used in combination with other HIV protease inhibitors to reduce LDL-cholesterol and triglyceride levels in AIDS patients undergoing protease inhibitor therapy while still maintaining the desired level of viral suppression.

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The appropriate dose of the HIV protease inhibitor being combined with atazanavir can be determined by the following method which was used for the atazanavir/saquinavir combination:

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Atazanavir is a moderate inhibitor of the cytochrome P450 3A enzyme comparable to nelfinavir and indinavir, with a K_i of 2.4 μM . The latter two compounds increase the exposure of saquinavir (dosed at 1200 mg thrice-daily (TID)) by 392 and 364%, respectively, at steady-state. A multiple-dose pharmacology study was completed to evaluate if a similar increase could be expected for the combination of atazanavir and saquinavir. This study showed a greater than 3-fold increase in exposure, due to combination with atazanavir, supporting a 1200 mg once-daily saquinavir dosing, was equivalent to the currently marketed saquinavir regimen of 1200 mg TID. Using a constant dose of atazanavir the range of saquinavir doses were studied to target the saquinavir exposure (AUC (area under the curve) and CMIN (minimum concentration)) similar to those in the literature. Similarly, appropriate dosing of other HIV protease inhibitors to be used in combination with atazanavir can be calculated.

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In another aspect, then, the present invention provides a method for reducing plasma LDL-cholesterol and/or triglyceride levels in an HIV-infected patient undergoing HIV protease inhibitor therapy which comprises administering to said patient an effective HIV-inhibiting amount of atazanavir in combination with an

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HIV-inhibiting amount of at least one HIV protease inhibitor metabolized by cytochrome P450 monooxygenase.

The present invention also provides pharmaceutical compositions comprising
5 an effective HIV-inhibiting amount of atazanavir and an effective HIV-inhibiting
amount of at least one other HIV protease inhibitor which is metabolized by
cytochrome P450 monooxygenase. Compositions in the form of capsules, tablets,
nasal sprays, solutions, powders, granules, emulsions, syrups, suppositories,
liposomes, suspensions, etc. such as those disclosed in U.S. Patent 6,166,004 are
10 suitable for the present invention.

CLAIMS

What is claimed is:

- 5 1. A method for reducing elevated plasma LDL and/or triglyceride levels in an HIV-infected patient resulting from therapy with one or more HIV protease inhibitors, comprising substituting an HIV-inhibiting and LDL and/or triglyceride reducing amount of atazanavir for the offending HIV protease inhibitor used in such therapy.
- 10 2. A method for reducing elevated plasma LDL and/or triglyceride levels in an HIV-infected patient undergoing HIV protease therapy which comprises administering to said patient an effective HIV-inhibiting amount of atazanavir in combination with an HIV-inhibiting amount of at least one HIV protease inhibitor
- 15 metabolized by cytochrome P450 monooxygenase.
3. The method of Claim 2 wherein atazanavir is administered in combination with an HIV protease inhibitor selected from saquinavir, indinavir, amprenavir, nelfinavir, tipranavir or lopinavir.
- 20 4. The method of Claim 3 wherein atazanavir is administered in combination with saquinavir.
5. A method for treating HIV infection in a patient exhibiting elevated plasma
- 25 LDL-cholesterol and/or triglyceride levels comprising administering to said patient an HIV-inhibiting amount of atazanavir.

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X**ABSTRACT**

A method for reducing elevated plasma LDL and/or triglyceride levels in an HIV-infected patient is disclosed. In this method, atazanavir (BMS-232632) can be used to treat HIV infection in patients exhibiting elevated plasma LDL-cholesterol and/or triglyceride levels, can be substituted for an offending HIV protease inhibitor used in such therapy, or can be used in combination with an HIV protease inhibitor metabolized by cytochrome P450 monooxygenase.

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

PTO-1382 (Rev. 4-1995) (Modified)

PCTUS2 FRP /REV03

Date	21-08-02
International Application No.	
Attorney Docket No.	CT-2879

I. Certification under 37 CFR 1.10 (if applicable)

EL 750820585US
Express Mail mailing number

21-08-02
Date of Deposit

I hereby certify that the application/correspondence attached hereto 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 Assistant Commissioner for Patents, Washington, D.C. 20231.

<i>David M. Morse</i>
Signature of person mailing correspondence

David M. Morse
Typed or printed name of person mailing correspondence

II. ☒ New International Application

TITLE	Use of Atazanavir in HIV Therapy
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Earliest priority date (Day/Month/Year)
31-08-01

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
- B. ☐ There is no prior U.S. application relating to this invention.
- C. ☒ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).

application no.	60/316,745	filed on	31 August 2001 (31.08.01)
application no.		filed on	

- D. ☐ The present international application ☐ is identical ☐ contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C.
- E. ☒ The present international application ☒ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages and ☒ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
- B. ☐ A Power of Attorney (General or Regular)
- C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

Priority document		Priority document	
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- E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☐ Other (please specify):

The person signing this form is the:

☐ Applicant
☒ Attorney/Agent (Reg. No.) 25,742
☐ Common Representative

David M. Morse
Typed name of signer
<i>David M. Morse</i>
Signature

U.S. Department of Commerce: Patent and Trademark Office

PC₁

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

F Receiving Office use only	
International Application No.	467
International Filing Date	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired) (12 characters maximum) CT-2879	

Box No. I TITLE OF INVENTION Use of Atazanavir in HIV Therapy	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BRISTOL-MYERS SQUIBB COMPANY P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America	
Telephone No. 800-252-4338	
Facsimile No. 800-252-4528	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BECHTOLD, Clifford M. 17 Streamview Circle Gulford, Connecticut 06437 United States of America	
This person is: ☐ applicant only ☐ applicant and inventor ☒ inventor only (If this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) MORSE, David M. Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America	
Telephone No. 203-877-8997	
Facsimile No. 203-877-8900	
Teleprinter No.	
Agent's registration No. with the Office 25,742	
☐ 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.V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|--|---|---|
| ☒ AE United Arab Emirates | ☒ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☒ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | |
| ☒ BB Barbados | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BG Bulgaria | ☒ KG Kyrgyzstan | ☒ SE Sweden |
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| ☒ CN China | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CO Colombia | ☒ LS Lesotho | ☒ TN Tunisia |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TR Turkey |
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| ☒ CZ Czech Republic | ☒ LV Latvia | |
| ☒ DE Germany | ☒ MA Morocco | ☒ TZ United Republic of Tanzania |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ UA Ukraine |
| ☒ DM Dominica | | ☒ UG Uganda |
| ☒ DZ Algeria | ☒ MG Madagascar | ☐ US United States of America |
| ☒ EC Ecuador | ☒ MK The former Yugoslav Republic of Macedonia | |
| ☒ EE Estonia | ☒ MN Mongolia | ☒ UZ Uzbekistan |
| ☒ ES Spain | ☒ MW Malawi | ☒ VN Viet Nam |
| ☒ FI Finland | ☒ MX Mexico | ☒ YU Yugoslavia |
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| ☒ GD Grenada | ☒ NO Norway | ☒ ZM Zambia |
| ☒ GE Georgia | | ☒ ZW Zimbabwe |
| ☒ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. 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. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 31 August 2001 (31-08-01)	60/316,745	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items
 ☒ item (1)
 ☐ item (2)
 ☐ item (3)
 ☐ item (4)
 ☐ item (5)
 ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(II)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA/ US.....

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | |
|---|--|---|
| ☐ Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| ☐ Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| ☐ Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| ☐ Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| ☐ Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

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Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets) : 4
 description (excluding sequence listing part) : 9
 claims : 1
 abstract : 1
 drawings : 0
 Sub-total number of sheets : 15

sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) : _____

Total number of sheets : 15

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801 (a)(i))(ii) ☐ in addition to being filed in paper form (under Section 801 (a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 5(ii), in right column):

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

1. ☒ fee calculation sheet : 1
 2. ☒ original separate power of attorney : 1
 3. ☐ original general power of attorney :
 4. ☐ copy of general power of attorney; reference number, if any: :
 5. ☐ statement explaining lack of signature :
 6. ☐ priority document(s) identified in Box No. VI as item(s): :
 7. ☐ translation of international application into (language): :
 8. ☐ separate indications concerning deposited microorganism or other biological material :
 9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))
 (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :
 (ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :
 (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column :
 10. ☐ other (specify): :

Number of items

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

English

Box No. X 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 request).

David M. Morse Agent
 David M. Morse

For receiving Office use only

1. Date of actual receipt of the purported international application:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 1(2):

5. International Searching Authority (if two or more are competent): ISA/

6. ☐ Transmittal of search copy delayed until search fee is paid

2. Drawings:

☐ received:☐ not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Applicant's or agent's
file reference

CT-2679

Date stamp of the receiving Office

Applicant

BRISTOL-MYERS SQUIBB COMPANY

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE

240.00 T

2. SEARCH FEE

700.00 S

International search to be carried out by US

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. DX applies, enter Sub-total number of sheets } 16
Where item (b) of Box No. DX does not apply, enter Total number of sheets }

b1 first 30 sheets 407.00 b1

b2 0 x 9.00 = 0.00 b2
number of sheets fee per sheetb3 additional component (only if sequence listing part of description
is filed in computer readable form under Section 801(a)(i), or both
in that form and on paper, under Section 801(a)(ii)):400 x = 0.00 b3
fee per sheet

Add amounts entered at b1, b2 and b3 and enter total at B 407.00 B

Designation Fees

The international application contains 100 designations.

5 x 88.00 = 440.00 D
number of designation fees amount of designation fee
payable (maximum 5)

Add amounts entered at B and D and enter total at I 847.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) 15.00 P

5. TOTAL FEES PAYABLE

1,802.00

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☒ authorization to charge ☐ postal money order ☐ cash ☐ coupons
☐ cheque ☐ bank draft ☐ revenue stamps ☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/ US

☒ Authorization to charge the total fees indicated above.

Deposit Account No.: 19-3800

☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Date: August 21, 2002

Name: David M. Morse

☐ Authorization to charge the fee for priority document.

Signature: David M. Morse

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

51
2
4

The undersigned applicant(s) (Names should be indicated as they appear in the request):

BRISTOL-MYERS SQUIBB COMPANY

hereby appoints (appoint) the following person as:



agent



common representative

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.)

ALGIERI, Aldo A.; BABAJKO, Suzanne; BELFIELD, Jing; BUCHHOLZ, Brian; D'AMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel J.; DUNCAN, Laurelee; FERGUSON, Blair; GIBBONS, Maureen; GODDARD, Christine; GOLIAN, Paul; HERMENAUE, Ronald S.; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; all of Bristol-Myers Squibb Company, P.O. Box 4000, Lawrenceville-Princeton Road, Princeton, New Jersey 08543-4000, United States of America

to represent the undersigned before



all the competent International Authorities



the International Searching Authority only



the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: Use of Atazanavir in HIV Therapy

Applicant's or agent's file reference: CT-2879

International application number (if already available):

filed with the following Office United States Patent and Trademark Office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; 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 request or this power):

David M. Morse
David M. Morse
Patent Counsel

Date: August 21, 2002

52
M
H

CERTIFICATION

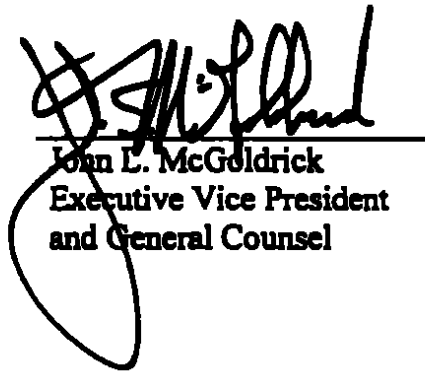
The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

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 22nd day of MAY 2002.

Balmer Ely
Secretary


John L. McGoldrick
Executive Vice President
and General Counsel

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

PTO-1382 (Rev. 4-1995) (Modified)

PCTUS2.FRP /REV03

Date	14-03-03
International Application No.	PCT/US02/28675
Attorney Docket No.	CT-2879

I. Certification under 37 CFR 1.10 (If applicable)

EL 750820387US
Express Mail mailing number

14-03-03
Date of Deposit

I hereby certify that the application/correspondence attached hereto 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 Assistant Commissioner for Patents, Washington, D.C. 20231.

<i>Warren K. Volles</i>
Signature of person mailing correspondence

Warren K. Volles
Typed or printed name of person mailing correspondence

II. ☐ New International Application

TITLE	
-------	--

Earliest priority date (Day/Month/Year)

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
- B. ☐ There is no prior U.S. application relating to this invention.
- C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).

application no.		filed on	
application no.		filed on	

- D. ☐ The present international application ☐ is identical ☐ contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C.
- E. ☐ The present international application ☐ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
- B. ☐ A Power of Attorney (General or Regular)
- C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

Priority document		Priority document	
-------------------	--	-------------------	--

- E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

- V. ☒ Other (please specify): PCT Demand for International Preliminary Examination;
PCT Demand Fee Calculation Sheet; Original Separate Power of Attorney

The person signing this form is the:

☐ Applicant	Warren K. Volles
☒ Attorney/Agent (Reg. No.) 33,810	Typed name of signer
☐ Common Representative	<i>Warren K. Volles</i> Signature

U.S. Department of Commerce: Patent and Trademark Office

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

PCT

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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	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference CT-2679	
International application No. PCT/US02/26675	International filing date (day/month/year) 21 August 2002 (21-08-02)	(Earliest) Priority date (day/month/year) 31 August 2001 (31-08-01)	
Title of invention Use of Atazanavir in HIV Therapy			
Box No. II APPLICANT(S)			
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.) BRISTOL-MYERS SQUIBB COMPANY P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America		Telephone No. 609-252-4338	
		Facsimile No. 609-252-4526	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: US		State (that is, country) of residence: 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.)			
State (that is, country) of nationality:		State (that is, country) of residence:	
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.)			
State (that is, country) of nationality:		State (that is, country) of residence:	
☐ Further applicants are indicated on a continuation sheet.			

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe 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
The address must include postal code and name of country.)VOLLES, Warren K.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
United States of America

Telephone No.

203-677-6997

Facsimile No.

203-677-8900

Teleprinter No.

Agent's registration No. with the Office
33,810☐ 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 | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

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

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☒ original separate power of attorney | 6. ☐ sequence listings in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listings |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

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).

 Agent
Warren K. Volles

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

<table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="width: 50%;">International application No.</td><td style="width: 50%;">PCT/US02/28675</td></tr><tr><td>Applicant's or agent's file reference</td><td>CT-2879</td></tr></table>	International application No.	PCT/US02/28675	Applicant's or agent's file reference	CT-2879	<table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="text-align: center;">For International Preliminary Examining Authority use only</td></tr><tr><td style="height: 100px; vertical-align: bottom; text-align: center;">Date stamp of the IPEA</td></tr></table>	For International Preliminary Examining Authority use only	Date stamp of the IPEA
International application No.	PCT/US02/28675						
Applicant's or agent's file reference	CT-2879						
For International Preliminary Examining Authority use only							
Date stamp of the IPEA							
Applicant							
CALCULATION OF PRESCRIBED FEES							
1. Preliminary examination fee	750.00 P						
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 as H is 25% of the handling fee.</i>)	137.00 H						
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	887.00 TOTAL						
MODE OF PAYMENT							
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash						
☐ cheque	☐ revenue stamps						
☐ postal money order	☐ coupons						
☐ bank draft	☐ other (specify):						
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs)							
☒ Authorization to charge the total fees indicated above.	IPEA/ <u>US</u>						
☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Deposit Account No.: <u>19-3880</u>						
	Date: <u>March 14, 2003</u>						
	Name: <u>Warren K. Volles</u>						
	Signature: <u><i>Warren K. Volles</i></u>						

PCT POWER OF ATTORNEY

1/1

CT-2679PCT

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 (updated 01.01.2003)
1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	BARAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; MAKUJINA, Shah; RYAN, Richard; VANATTEN, Mary, K.; VOLLES, Warren, K.; KORSEN, Elliott; LAMERDIN, John Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 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	USE OF ATAZANAVIR IN HIV THERAPY
1-4-2	Applicant's or agent's file reference	CT-2679PCT
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	<i>Richard P. Ryan</i>
2-1-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-1-2	Name of signatory	Richard P. Ryan
2-1-3	Capacity	Senior Patent Counsel
3	Date	14 March 2003 (14.03.2003)

59 16

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 22nd day of May 2002.

Balme Bly
Secretary

John L. McGoldrick
Executive Vice President
and General Counsel

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

APR 24 2003

To:
DAVID M. MORSE
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

RECEIVED

BMS PATENT LAW

PCT WALLINGFORD, CT.

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

APR 18 2003

Docketed Item

US-1DS

(PCT Rule 44.1)

Due Date 7/15/03

Date of Mailing
(day/month/year)

15 APR 2003

Attorney (L.H.)

Applicant's or agent's file reference
CT-2679

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US02/26675

International filing date
(day/month/year)

21 August 2002 (21.08.2002)

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
Commissioner for Patents
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer

Valerie Bell-Harris for
Zohreh Fry

Telephone No. 703-308-1235

Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference CT-2679	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/26675	International filing date (day/month/year) 21 August 2002 (21.08.2002)	(Earliest) Priority Date (day/month/year) 31 August 2001 (31.08.2001)
Applicant 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 4 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/US02/26675

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 1-2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/26675

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/7072, 551

US CL : 514/50, 220

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. : 514/50, 220

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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	Database MEDLINE on STN, No. 2003007811, SANNE et al. 'Results of a Phase 2 Trial of Atazanavir at Three Doses in Combination with Didanosine and Stavudine in Antiretroviral-Naive Subject,' abstract, JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, 2003, 32 (1) 18-29.	1, 3-5
A	Database CAPLUS on STN, No. 2002:891974, DE CLERCQ, ERIK. 'New Anti-HIV Agents and Targets,' abstract, Medicinal Research Reviews, 2002, 22(6), 531-565.	1, 3-5



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

06 March 2003 (06.03.2003)

Date of mailing of the international search report

15 APR 2003

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Valerie Bell-Hamilton
Colleen Fay

Telephone No. 703-308-1235

INTERNATIONAL SEARCH REPORT

PCT/US02/26675

64

Continuation of Box I Reason 2:

Present claim 2 relates to compounds defined by reference to a desirable characteristic or property, namely "HIV protease inhibitors". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only very limited number of such compounds. Moreover, the claimed combination, namely "one or more HIV protease inhibitors" in combination with atazanavir covers numerous possible combinations. In the present case, the claims so lack support, and the applications so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again this search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in the examples specified in claim 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT).

Continuation of B. FIELDS SEARCHED Item 3:

STN ONLINE

search terms: HIV protease inhibitors, LDL cholesterol, triglyceride, lipoprotein, atazanavir, saquinavir, indinavir, amprenavir, nelfinavir, tipranavir, lopinavir

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/26675

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/7072, 551
US CL : 514/50, 220

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. : 514/50, 220

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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	Database MEDLINE on STN, No. 2003007811, SANNE et al. 'Results of a Phase 2 Trial of Atazanavir at Three Doses in Combination with Didanosine and Stavudine in Antiretroviral-Naive Subject,' abstract, JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, 2003, 32 (1) 18-29.	1, 3-5
A	Database CAPLUS on STN, No. 2002:891974, DE CLERCQ, ERIK. 'New Anti-HIV Agents and Targets,' abstract, Medicinal Research Reviews, 2002, 22(6), 531-565.	1, 3-5

☐ 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

"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

06 March 2003 (06.03.2003)

Date of mailing of the international search report

15 APR 2003

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer
Valerie Bell-Hannafor
Colleen Fry

Telephone No. 703-308-1235

INTERNATIONAL SEARCH REPORT

International application No. ,

PCT/US02/26675

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 1-2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/26675

66
X
10

Continuation of Box I Reason 2:

Present claim 2 relates to compounds defined by reference to a desirable characteristic or property, namely "HIV protease inhibitors". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only very limited number of such compounds. Moreover, the claimed combination, namely "one or more HIV protease inhibitors" in combination with atazanavir covers numerous possible combinations. In the present case, the claims so lack support, and the applications so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again this search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in the examples specified in claim 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT).

Continuation of B. FIELDS SEARCHED Item 3:

STN ONLINE

search terms: HIV protease inhibitors, LDL cholesterol, triglyceride, lipoprotein, atazanavir, saquinavir, indinavir, amprenavir, nelfinavir, tipranavir, lopinavir

AS: 93165
067

APOSTILLE

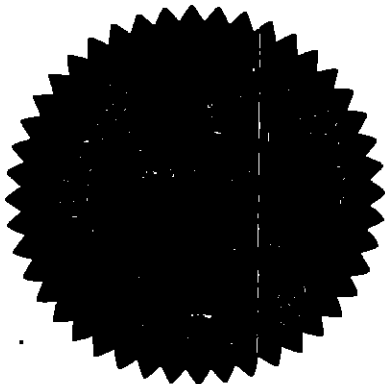
(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

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

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 14TH DAY OF JANUARY 2004
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A190043
9. SEAL/STAMP:
10. SIGNATURE

John E McCormac



68
16

I, Stephen B. Davis, Patent Counsel, Patent Department, Bristol-Myers Squibb Company

do hereby certify that this document is a notarized true and accurate copy of the original assignment signed by the inventors.

Stephen B. Davis
Stephen B. Davis

STATE OF New Jersey

:

ss.

COUNTY OF Mercer

:

Subscribed before me on this 6th day of January, 200 4

Diane C. Bartram
Notary Public

(SEAL)

DIANE C. BARTRAM
Notary Public of New Jersey
My Commission Expires March 8, 2005



69
X

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

DECEMBER 24, 2003

PTAS

700057884

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

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: 12/22/2003

REEL/FRAME: 014217/0062
NUMBER OF PAGES: 4

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

ASSIGNOR:

BECHFOLD, CLIFFORD

DOC DATE: 08/30/2001

ASSIGNEE:

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

SERIAL NUMBER: 60316745
PATENT NUMBER:

FILING DATE: 08/31/2001
ISSUE DATE:

ANTHONY ROYALL, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

DEC. 22, 2003 4:01 PM

BPS PATENT 283 573 5988

NO. 028 P. 2

FORM PTO-1588
(Rev. 8-00)

RECORDATION FORM COVER SHEET

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

OMB No. 0981-0011 (exp. 4-04)

PATENTS ONLY

To the Honorable Director of the US Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Clifford Beachfold

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

Execution Date: 8/30/01

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

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)

60318,745

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 2.41)

\$ 40

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

8. Deposit account number:

18-3880 (in the name of Bristol Myers Squibb Company)

(Attach duplicate copy of this page if bridge or 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.

Warren Volles
Name of Person Signing
Reg. No. 88,810

Signature

December 22, 2003
Date☐ Certificate of mailing on reverse side

Total number of pages including cover sheet, attachments, and documents: 2

Mail documents to be recorded with required cover sheet information to:
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PO Box 1480, Alexandria, VA 22313-1480

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):

Clifford M. Bechtold

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 _____

Execution Date: _____

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

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)

60/316,745

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

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

Name: Marie J. Mathias

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:

19-3880 (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.

David M. Morse

Name of Person Signing
Reg. No. 25,742

David M. Morse
Signature

August 31, 2001
Date

☐ Certificate of mailing on reverse side

Total number of pages including cover sheet, attachments, and document: 2

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

ASSIGNMENT

72
A

I,

Clifford M. Bechtold

residing at

17 Streamview Circle
Guilford, Connecticut 06437
United States of America,

pursuant to contractual obligations heretofore assumed by me 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 my right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to me 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:

Use of Atazanavir in HIV Therapy

invented by me and described in the provisional United States patent application executed on even date herewith 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 me if this sale, assignment and transfer had not been made;

And I hereby agree to communicate to said assignee or its representatives any facts known to me 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 30th day of August, 2001 by Clifford M. Bechtold
Clifford M. Bechtold

24. 1

ACKNOWLEDGMENT

State of Connecticut)

ss: Wallingford

County of New Haven)

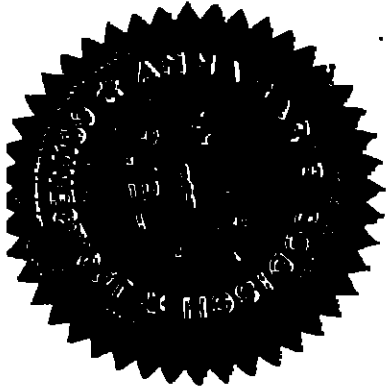
On this 30th day of August 2001, before me
_____, the undersigned, personally appeared Clifford M. Bechtold,
to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and
acknowledged that he executed it.

Annamarie Bodisch
Notary Public

(Seal)

COMMISSION EXPIRES: _____

ANNAMARIE BODISCH
Notary Public
My Commission Expires March 31, 2005



75 76

04-012030

ISUPERINDUSTRIA Y COMERCIO

SISTEMA DE REGISTRO

Fecha 24/02/2004

MANTENIMIENTO DE PROTOCOLOS

Numero : 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 Secv: 0 Seac: 0

Isencia Codigo Ctr

Nombre

1 340 A CASTRO DUQUE RAMIRO

2 3002 GOMEZ MEJIA HECTOR

Encontrados (1/1) registro(s)

76 74

SUPERINDUSTRIA Y COMERCIO

Radicacion 04812030 00000000 Folios 75
Fecha (MM): 2004-02-12 10:09 25
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓	()	() ✓
MODELO DE UTILIDAD	()	() ✓
Indicacion de que se solicita la concesion 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 grafica y fotografica del Diseño Industrial o muestra del Material que incorpora el diseno	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
Indicacion de que solicita el registro de un Esquema de trazado	()	()
Datos de identificación del solicitante o de la persona que presenta La solicitud	()	()
Representacion grafica del esquema de trazado	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable



Fecha



Folio 78

2020
Bogotá DC

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

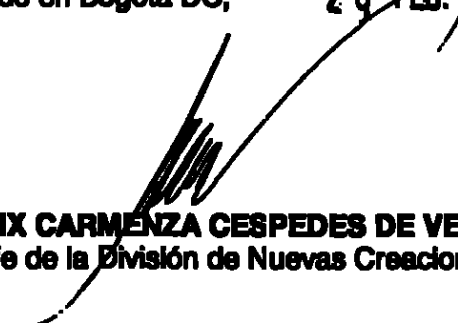
REFERENCIA:	Radicación No.	04-12030
	Solicitud Internacional	PCT/US02/26675
	Fecha inicio fase nacional	31/03/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	330
	Folios	001

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 la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase

Dado en Bogotá DC,

26 FEB. 2004


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202060