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Señora Jefe de la
DIVISION DE SIGNOS DISTINTIVOS
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011 Evento : 379 Actuación : 467

Referencia : Expediente No. 05.070.211
Asunto : Oposición a la solicitud de patente para: **USO DE UNA ASOCIACIÓN QUE CONTIENE UN INHIBIDOR NO NUCLEÓSIDO DE LA TRANSCRIPTASA INVERSA (NNRTI) CON UN INHIBIDOR DE CITOCROMO P450, TALES COMO LOS INHIBIDORES DE LA PROTEASA**
Solicitante : **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
Opositor : **PROCAPS S.A.**

1. Yo, Emilio FERRERO, obrando como apoderado de la sociedad solicitante en el asunto identificado en la referencia, solicito a usted, que en virtud de lo establecido en el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, otorgue a favor de mi representada un plazo adicional de sesenta (60) días para atender el Oficio No. 11334 notificado por fijación en lista del 14 de septiembre de 2007.

2. Para efectos de la extensión del término presento con este memorial, el recibo expedido por el Fondo Especial de la Superintendencia de Industria y Comercio, en donde consta el pago realizado por valor de \$72.000,00, de conformidad con lo dispuesto en la Resolución No. 36155 del 28 de diciembre de 2006.

Señora Jefe,



EMILIO FERRERO

T.P.A. N° 31.929

COLO 09255-841-017-8
COLO-09255-264-001-0
JGG\JGG\ID-114238\WPCL9255
No. M-2007-114238\JGG

096 09255-264-0010

RECIBO DE CASH APLICADO AL EXPEDIENTE No.

RESPONSABLE :

SOL: SESENTA Y DOS MIL PESOS

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72,000.00 \$ TOTAL : 72,000.00

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***** C O N C E P T O *****

CAVELIER ASOBADOS COMISIONACION BANCO POPULAR 050-00110-6 +0825361 03/12/2007 68,288,000.00

DEPOSITANTE TIPO PAGO BANCO CUENTA NO. PAGO FECHA PAGO VT. PAGO

***** C O M I S I O N A C I O N *****

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Using Pharmacokinetics to Optimize Antiretroviral Drug-Drug Interactions in the Treatment of Human Immunodeficiency Virus Infection

John G. Gerber

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Better understanding of the pharmacokinetics of antiretroviral drugs has resulted in the design of combination therapies for the treatment of human immunodeficiency virus (HIV) infection. This has improved the bioavailability and prolonged the plasma half-life of some of the drugs, resulting in enhanced antiviral activity. However, antiviral combination therapy can also result in adverse drug-drug interactions and diminished antiretroviral activity. In this review, we examine drug interactions involving combinations of protease inhibitors, combinations of protease inhibitors with nonnucleoside reverse transcriptase inhibitors, and combinations of nucleoside analogues for the treatment of patients with HIV infection. We discuss examples and mechanisms of pharmacokinetic interactions that improve or decrease antiviral efficacy.

The use of multidrug therapy for HIV infection makes it imperative to understand how antiretroviral drugs interact with one another. Antiretroviral drug combinations can result in pharmacokinetics that are favorable, unchanged, or adverse.

There are presently 14 antiretroviral drugs on the market. Six of them are nucleoside reverse transcriptase inhibitors (NRTIs): zidovudine, didanosine, stavudine, zalcitabine, lamivudine, and abacavir. Three are nonnucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine, delavirdine, and efavirenz. Five are protease inhibitors (PIs): saquinavir, ritonavir, indinavir, nelfinavir, and amprenavir.

To understand how antiretroviral drugs interact with each other, a knowledge of their pharmacokinetics is an absolute necessity. Pharmacokinetics are simply what the body does to a drug when it is administered by any route. Pharmacokinetics for an orally administered drug include its absorption, first-pass metabolism, distribution, metabolism (either activation or inactivation), and elimination. Bioavailability is the term that defines the fraction of the drug that reaches the systemic circulation after oral administration. Low bioavailability can be the result of poor absorption as well as extensive first-pass metabolism.

For a drug to traverse the intestinal epithelial membrane, it must be in solution in the aqueous milieu of the gastrointestinal tract and be sufficiently lipophilic to pass through lipid membranes. The vast majority of antiretroviral drugs undergo passive diffusion through the gastrointestinal lining, driven by a

concentration gradient. Once in the intestinal epithelial cells, lipophilic drugs can be transported back to the luminal surface by the P-glycoprotein [1], a multidrug-resistance-transport protein, and/or metabolized by the intestinal cytochrome P450 (CYP) 3A isoenzymes [2]. The exact mechanisms by which the CYP enzymes interact with P-glycoprotein to adversely affect the bioavailability of drugs are currently unclear. It has been noted, however, that many drugs with a high affinity for CYP3A are also substrates for the P-glycoprotein [3]. Once in the portal circulation, drugs can be further metabolized by the liver before they reach the systemic circulation.

In the systemic circulation, drugs are distributed into tissues on the basis of their relative affinity for tissue components versus plasma components. Drugs with high affinity for tissue proteins have a large volume of distribution because of their preferential partitioning into tissues. Most lipophilic drugs are attracted to plasma proteins; therefore, plasma concentrations of drugs are a composite of both bound and free drugs. At steady state, the free drug is in equilibrium with the intracellular compartment as long as the drug enters the cells by simple diffusion and is not actively pumped out of the cytoplasm.

Therefore, total plasma concentration of a drug may be an underestimation of the actual concentration necessary for an effect. This has certainly been observed with the lipophilic HIV PIs. For example, the HIV PI SC-52151 becomes highly protein-bound, such that effective free concentrations are not achievable despite seemingly high total plasma concentrations [4]. It has been proposed that in the CNS, P-glycoprotein-mediated efflux in brain capillary endothelial cells inhibits the accumulation of HIV PIs at this site [5, 6].

Drugs in the systemic circulation are usually metabolized or excreted unchanged. Lipophilic drugs, such as PIs and NNRTIs, are oxidatively metabolized by the CYP enzymes to more polar forms for subsequent biliary or renal excretion. CYPs are a group of heme-containing membrane-bound en-

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Ritonavir may inhibit both intestinal and hepatic CYP3A4 and thus improve the bioavailability of saquinavir by decreasing its systemic clearance. The combination of ritonavir and saquinavir (400 mg/400 mg) appears to have extremely potent antiretroviral activity, judged on the basis of the documented durable responses observed in patients [20]. It is unclear how much ritonavir contributes to the antiviral effect of the high concentration of saquinavir. This is an important question, because ritonavir is poorly tolerated at high doses. However, there are only limited pharmacokinetic data on single low doses of ritonavir with saquinavir.

In healthy volunteers, ritonavir increases saquinavir exposure in a dose-dependent manner [17]. More important, there are no efficacy data on low-dose ritonavir combined with saquinavir. Lower and better-tolerated doses of ritonavir may make this combination more attractive as therapy. However, before a lower dose of ritonavir can be recommended for use with saquinavir, we need comparative efficacy data from studies with adequately large sample sizes.

Indinavir is a potent and relatively well-tolerated PI. The drug has some pharmacokinetic advantages over the other PIs but many disadvantages as well. The main advantage is that only 60% of indinavir is protein-bound in the circulation. At steady state, the total plasma concentration of the drug therefore may more closely reflect the diffused intracellular concentration, which is important for its antiretroviral effects [21]. However, the drug has numerous pharmacokinetic disadvantages. Indinavir has to be taken on an empty stomach or with a low-fat snack [22]. The drug has a very short half-life because of the high systemic clearance; therefore the present recommended dose is 800 mg every 8 h.

Because of the large variability in both bioavailability and systemic clearance, the trough concentration of indinavir can vary widely across a patient population and sometimes can fall significantly below the 95% inhibitory concentration [23]. In addition, because of the rigid dosing schedule and the dietary requirement for maximal absorption, drug adherence can be difficult. Inadequate plasma concentrations of indinavir may promote the evolution of PI-resistant strains of HIV. Indinavir is also the only PI with significant renal excretion [24]. Since the drug has limited water solubility, especially at higher urinary pH, a significant proportion of patients who take indinavir may develop nephrolithiasis. It has been shown that the urinary concentration of indinavir directly correlates with its plasma concentration; thus, during the first 3–4 h after drug administration, the urine becomes supersaturated with indinavir [22].

The administration of ritonavir improves the bioavailability and prolongs the elimination half-life of indinavir, and it reduces the total dose necessary to achieve a potent antiretroviral plasma concentration. There are accumulating and encouraging clinical data concerning the combination of ritonavir and indinavir. The pharmacokinetic interaction study findings in normal volunteers were very positive [25]. Ritonavir (400 mg twice

daily) decreases the systemic clearance and improves the oral bioavailability of indinavir to the point that a lower dose of indinavir (400 mg twice daily) results in the same drug exposure as a high dose (e.g., 800 mg every 8 h). The trough concentration of indinavir is also consistently higher with the ritonavir/indinavir combination than with indinavir alone. Most surprising is that food does not affect the bioavailability of indinavir when it is administered with ritonavir [26]. With the lower peak concentration of indinavir resulting from administration of the lower dose, the incidence of renal stone formation may be reduced.

Recently, pharmacokinetic data were presented about variable dosage combinations of indinavir and ritonavir. Burger et al. [27] treated antiretroviral-naïve, HIV-infected patients with a combination of indinavir (800 mg) and ritonavir (100 mg) b.i.d. and found that the trough concentration of indinavir was 4-fold higher than with the regimen of indinavir alone, 800 mg every 8 h. This combination was well tolerated and was significantly less expensive because fewer pills were administered. Saah et al. [28] administered varying dosage combinations of indinavir and ritonavir to healthy volunteers. They found that ritonavir had a favorable and dose-dependent effect on indinavir pharmacokinetics. At a dosage combination of 800 mg of indinavir and 200 mg of ritonavir b.i.d., the trough concentration of indinavir was very high.

Efficacy and toxicity data are urgently needed concerning this unique PI dosage combination. The only clinical data on a combination of these PIs (at a dose of 400 mg/400 mg) with 2 NRTIs have been presented by Workman et al. [29] and Rockstroh et al. [30] and demonstrated excellent antiviral efficacy in PI-naïve patients. These data, however, should be interpreted with caution since these were not comparative trials and indinavir with 2 NRTIs can be a very potent antiretroviral drug combination.

There are some data on the pharmacokinetics of nelfinavir in combination with ritonavir. Since both ritonavir and nelfinavir are potent inducers of microsomal drug-metabolizing enzymes, it is important they be at steady state when drug-drug interactions between these PIs are evaluated. It usually takes 10–14 days to maximally induce metabolism of these drugs. In normal volunteers, ritonavir has been shown to increase nelfinavir exposure 2-fold to 3-fold. Flexner et al. [31] examined the effect of ritonavir (400 mg twice daily) on the kinetics of 2 doses of nelfinavir and its active metabolite, M8 (AG-1402), in HIV-infected patients. Using historical controls for comparisons, they found that ritonavir increased nelfinavir exposure approximately 2-fold but increased the generation of M8 3- to 4-fold.

These data suggest that the inductive effect of ritonavir on CYP2C19 may be substantially greater than its inhibitory activity. Although clinical data were difficult to interpret because of an inadequate sample size, this combination does not appear

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Table 2. Drug interactions of protease inhibitors in combination with nonnucleoside reverse transcriptase inhibitors (NNRTIs).

Drug combination	Pharmacokinetic effect	Virological outcome
Delavirdine and indinavir	Increased indinavir exposure (~50%), resulting in lower dose of indinavir	Mostly uncontrolled studies, but appeared to have some efficacy for salvage therapy after multidrug failure
Nevirapine and indinavir	Decreased indinavir exposure (~30%) but diminished variability in C_{min} ; increased dose of indinavir is recommended	Excellent antiretroviral effect
Nevirapine and nelfinavir	No change in kinetics of either drug	Excellent antiretroviral effect
Efavirenz and indinavir	Decreased indinavir exposure (~30%); increased dose of indinavir is recommended	Excellent and durable antiretroviral effect

NOTE. C_{min} , minimal concentration of drug.

to be as efficacious as either ritonavir/saquinavir or ritonavir/indinavir [32].

Other combinations of PIs have not yielded sufficient clinical or pharmacokinetic data for full interpretation. However, nelfinavir clearly has been found to increase the exposure of saquinavir, but to a lesser degree than ritonavir does [33].

Drug-Drug Interactions of PIs and NNRTIs

The combination of PIs and NNRTIs (table 2) is attractive because both groups of drugs have potent antiretroviral efficacy and they are not antagonistic. Of the NNRTIs, delavirdine is the largest by molecular weight, and it has been used extensively in clinical trials. Delavirdine is metabolized by multiple CYPs, but it inhibits CYP3A4 significantly [34]. Delavirdine inhibits the metabolism of the PIs, thereby increasing the AUC of indinavir, ritonavir, and nelfinavir by 50%–80%. It notably increases saquinavir exposure, by >400% [35, 36]. The dose of indinavir is recommended to be reduced to 600 mg every 8 h because of the inhibitory effect of delavirdine. Indinavir, saquinavir, and ritonavir do not affect the kinetics of delavirdine metabolism [37]. In contrast, both rifampin and rifabutin, potent inducers of CYP3A4 and 2C9, stimulate the metabolism of delavirdine, suggesting the involvement of CYP3A4 and CYP2C9 [38, 39]. Since ritonavir inhibits CYP3A4 and likely induces CYP2C9, the combined effect of these activities may not alter the pharmacokinetics of delavirdine.

In contrast, nelfinavir decreases the AUC of delavirdine by 50% [40]. This effect is probably secondary to the ability of nelfinavir to induce the activity of multiple microsomal enzymes. Large clinical trials with this drug combination have been limited, but the report of an uncontrolled study suggested that the combination of indinavir or nelfinavir with delavirdine has antiviral efficacy in patients for whom other antiretroviral drugs have failed [41].

Of the antiretroviral drugs, nevirapine and efavirenz have favorable pharmacokinetics because of their long plasma half-life. The weakness of all of the NNRTIs as antiretroviral drugs, however, is that HIV rapidly develops resistance to these agents.

Nevirapine has a small molecular weight, predictably good bioavailability, and because of its low hepatic clearance, a long half-life [42]. Protein binding is only 60%, and the drug distributes to multiple sites, including the CNS [43]. Hepatic metabolism of nevirapine is mainly through the activity of CYP2B6 and CYP3A4. Nevirapine induces its own metabolism by activating both CYP2B6 and CYP3A4. The induction of these enzymes appears to result in an interaction of nevirapine with PIs, since the AUCs of both indinavir and saquinavir are decreased by nevirapine by ~28% [44, 45].

In the presence of nevirapine, therefore, the present recommendation is to increase the dose of indinavir to 1000 mg every 8 h. Nevirapine has no significant effect on the pharmacokinetics of either ritonavir or nelfinavir, perhaps because these drugs induce their own metabolism [46]. No PI has a significant effect on the pharmacokinetics of nevirapine, a circumstance suggesting that CYP3A4 does not have a major role in the metabolism of nevirapine. Data from clinical trials with the combination of PIs and nevirapine indicate this combination to be potent [47, 48].

Efavirenz is the latest of the NNRTIs to be approved by the US Food and Drug Administration for clinical use (September 1998). It is the most potent of the NNRTIs and has shown remarkable efficacy when combined with 2 NRTIs [49]. When efavirenz is combined with indinavir, it also causes a potent and durable antiretroviral effect [50]. Efavirenz has favorable pharmacokinetics. It is efficiently absorbed and has a very long half-life; therefore, once-a-day administration is recommended. The drug is metabolized in the liver mainly by CYP2B6 and CYP3A4.

Like nevirapine, efavirenz also induces its own metabolism. Induction of CYP3A4 by efavirenz results in enhanced metabolism of indinavir, saquinavir, and amprenavir. In clinical trials, the dose of indinavir has been increased to 1000 mg every 8 h to compensate for the ~30% decrease of the AUC when the drug is combined with efavirenz [51]. Efavirenz has a greater effect on the metabolism of saquinavir than on that of indinavir, so it is not currently recommended for use with saquinavir.

In addition to stimulating CYP3A4, efavirenz inhibits

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Table 3. Drug interactions of nucleoside reverse transcriptase inhibitors used in combination.

Drug combination	Pharmacokinetic effect	Virological outcome
Stavudine and zidovudine	Decreased intracellular phosphorylation of stavudine	Loss of stavudine activity; the combination should not be used
Lamivudine and zalcitabine	Decreased intracellular phosphorylation of lamivudine	No data; the combination probably should not be used
Didanosine and hydroxyurea	Increased phosphorylation of dideoxyadenosine	Enhanced antiviral activity

CYP2C19. Therefore, the combination of efavirenz and nelfinavir may cause a small but significant increase in the AUC of nelfinavir and a significant decrease in the formation of its active metabolite, M8 [12]. Efavirenz also slightly but significantly increases ritonavir exposure. The effect of the PIs on efavirenz pharmacokinetics has generally been found to be insignificant, although recently it has been reported that the AUC of efavirenz increases slightly when it is combined with ritonavir [52].

Finally, the importance of pathways for efavirenz metabolism, other than those mediated by CYP3A4, have been suggested by data showing that rifampin decreased efavirenz exposure inconsistently and only to a minor extent [53].

Drug-Drug Interactions of NRTIs Used in Combination

For the NRTIs, adverse or favorable drug interactions occur at the level of phosphorylation. All of the NRTIs are prodrugs that require activation by 3 cellular phosphorylation steps to form a triphosphate derivative, which then competes with endogenous nucleotides for viral reverse transcriptase. With the use of multiple NRTIs in the clinical treatment of HIV infection (table 3), it is important to understand how these drugs interact at the level of intracellular phosphorylation.

Stavudine and zidovudine are thymidine analogues that share intracellular phosphorylation pathways. In addition, zidovudine monophosphate accumulates in cells in high concentrations because of its ability to inhibit thymidylate kinase, thereby slowing further phosphorylation [54]. Stavudine, in the presence of zidovudine, is very poorly phosphorylated, probably because it does not compete effectively with zidovudine at the thymidine kinase step, and further phosphorylation is slowed by the inhibition of thymidylate kinase by zidovudine monophosphate [55]. Clinical evaluation of the combination of stavudine and zidovudine administered to patients who had previously received zidovudine therapy was conducted in AIDS Clinical Trials Group (ACTG) 290. That study demonstrated that the virological outcome for patients receiving both drugs was poorer than the outcome for patients receiving stavudine alone [56].

Zalcitabine and lamivudine, both cytosine analogues, use the same phosphorylation pathways and adversely affect the phosphorylation of each other in vitro [57]. Since zalcitabine is given to patients only infrequently, clinical correlations of these in vitro adverse drug-drug interactions have not been reported.

However, these 2 drugs should not be used together to treat HIV infection.

Finally, hydroxyurea, a ribonucleotide reductase inhibitor, improves the phosphorylation and the activity of numerous NRTIs, most prominently didanosine [58, 59]. The use of hydroxyurea has been shown in clinical trials to improve the efficacy of didanosine administered with stavudine [60].

In summary, with the use of multiple antiretroviral drugs for the treatment of HIV infection, it is critical to understand their pharmacokinetic interactions so that favorable effects are optimized and adverse ones avoided. This review has discussed examples of both types of interactions in the multidrug treatment of HIV infection.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/EP2003/014224
Fecha de Presentación Internal. 15-12-2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 58 a 69 (como se radicó inicialmente)
- 1.2. Reivindicaciones: Folios 70 a 72 (como se radicó inicialmente)
- 1.3. Oposiciones: Folios 82 a 91
 Nombre del opositor: Laura Catalina Silva Barrera.
 PROCAPS S.A.
- 1.4. Prioridad: Folio: 1
 Fecha: 16-12-2002; país y número: US 60/433.690.

2. Objeto de la invención

Título de la solicitud: "USO DE UNA ASOCIACIÓN QUE CONTIENE UN INHIBIDOR NO NUCLEÓSIDO DE LA TRANSCRIPTASA INVERSA (NNRTI) CON UN INHIBIDOR DE CITOCROMO P450, TALES COMO LOS INHIBIDORES DE LA PROTEASA".

El problema planteado en esta solicitud es la necesidad de minimizar el metabolismo del compuesto de fórmula (I) por el citocromo P450.

Para solucionar este problema técnico la solicitud en estudio propone la administración conjunta de un inhibidor de citocromo P450, especialmente un inhibidor de CYP3A4.

Clasificación Internacional de Patentes (IPC.) como: A61K 31/55, A61K 31/427, A61P 31/18.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

Las reivindicaciones 1 a 8 reclaman "una asociación". Solo se otorgan patentes a las invenciones de producto y procedimiento, y una asociación no corresponde a ninguna de las dos.

La reivindicación 1, hace referencia a un compuesto de fórmula (I), este compuesto debe presentarse en el capítulo reivindicatorio, no se admite hacer referencia a la descripción.

Las reivindicaciones no cumplen con el requisito de definición, claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)

Las reivindicaciones 11, 17, 19 y 21 a 25 reclaman métodos para tratar una enfermedad. Estas reivindicaciones no son patentables.

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Las reivindicaciones 12 a 16, 18 y 20 reclaman el uso de una asociación. Estas reivindicaciones no son patentables.

6. Unidad de invención (artículo 25 D 486)

La reivindicación 10 reclama un estuche de partes que comprende una asociación. El estuche reclamado posee diversos componentes que se encuentran contenidos en campos técnicos diferentes, por lo cual esta reivindicación carece de unidad de invención ya que no conforma un único concepto inventivo.

7. Análisis de la(s) Oposición(es): (artículo 43 D. 486):

El opositor presenta los siguientes documentos como anterioridades:

- D1: WO9844913
- D2: WO0196338.
- D3: US6391919.

El opositor establece que la presente solicitud a la luz de D1 a D3 carece de novedad. Esta oficina difiere de la afirmación del opositor toda vez ninguna de las anterioridades presentadas divulga todas las características técnicas de la invención reclamada; se remite al opositor al artículo 16 de la Decisión 486, en donde se define novedad, debido a que las anterioridades no comprenden en su totalidad la invención reclamada esta oficina establece que las mismas no afectan la novedad.

Para el examen de patentabilidad de la presente solicitud, esta oficina encuentra relevante el documento D2, por presentar el compuesto de fórmula (I) útil como un inhibidor de la transcriptasa reversa no nucleósido.

8. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: 16-12-2002.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación
D2	WO01/96338	NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	20-12-2001
D4	Clinical Infectious Diseases 2000;30(suppl 2): S123-9	USING PHARMACOKINETICS TO OPTIMIZE ANTIRETROVIRAL DRUG-DRUG INTERACTIONS IN THE TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION	2000

9. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

El documento del Estado de la Técnica más próximo es D4 que enseña los beneficios de la terapia combinada ritonavir con NNRTIs que son metabolizados por CYP3A4.

La única diferencia con D4 es que esta solicitud menciona una composición farmacéutica que contiene como NNRTI el compuesto de la fórmula (I). Pero esta diferencia no concede un efecto técnico inesperado porque D4 enseña que el ritonavir es inhibidor de CYP3A4 que mejora la actividad de los NNRTI que son metabolizados por esta vía. (pág. 125 col. derecha párrafo 1).

El problema técnico planteado en esta solicitud es la necesidad de minimizar el metabolismo del compuesto de fórmula (I) por el citocromo P450. Este problema se había resuelto previamente mediante la combinación con agentes inhibidores del citocromo P450, D4 enseña que el ritonavir y nelfinavir disminuyen el metabolismo del Delavirdin y Efavirenz (páginas 126 y 127). Adicionalmente se establece que el AUC del efavirenz se incrementa con el ritonavir (pág 127 párrafo 1).

Además D2 divulgaba previamente el compuesto de la fórmula (I) (reiv. 1 y 7), esta anterioridad enseña que este compuesto es un inhibidor de la transcriptasa reversa no nucleósido (abstract); D2 también enseña que el compuesto de la fórmula (I) puede administrarse en un rango de 0.1mg a 800mg por día a una persona de 70 kg (pág. 7 líneas 19 a 23). En consecuencia, una persona conocedora de la materia motivada por las enseñanzas de D2 y D4 lograría las composiciones de esta solicitud. Por lo cual las reivindicaciones 1- 9 no tiene Nivel Inventivo.

9. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D2	WO01/96338	1-9	Nivel Inventivo
D4	Clinical Infectious Diseases 2000;30(supl 2): S123-9	1-9	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL

Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

CONCEPTO TÉCNICO No. 18	EXAMINADOR TÉCNICO Código No. 202073
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