

REYES & REYES

A B O G A D O S

132 1 de 66
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-089792- -00005-0000

Fecha: 2008-11-25 16:23:50 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 66

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 07-089-792

TÍTULO SOLICITADO: UNA FORMULACIÓN SÓLIDA DE DOSIFICACIÓN FARMACÉUTICA.

PUBLICACIÓN: Gaceta: 592 de 30/05/2008, N° de publicación: 458.

PRIORIDAD: US 11/064,467 de 23/02/2005

SOLICITANTE: ABBOTT LABORATORIES.

APODERADO: ALICIA LLOREDA RICAURTE.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comendidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

La solicitud colombiana 07-079-737 que reivindica una forma de dosificación farmacéutica que comprende una forma no disuelta de Lopinavir o lopinavir/ritonavir en una cantidad adecuada para uso terapéutico, carece de novedad y nivel inventivo como se argumenta a continuación:

➤ En primer término, existen publicaciones de carácter científico que demuestran la previa existencia de la combinación farmacológica entre lopinavir y ritonavir para el tratamiento de pacientes infectados con el VIH, veamos:

✓ **Lopinavir/Ritonavir: A Review Of Its Use In The Management Of HIV Infection¹.**

Abstract: *Lopinavir is a novel protease inhibitor (PI) developed from ritonavir. Coadministration with low-dose ritonavir significantly improves the pharmacokinetic properties and hence the activity of lopinavir against HIV-1 protease. Coformulated lopinavir/ritonavir was developed for ease of administration and to ensure both drugs are taken together, as part of combination therapy with other antiretroviral agents. Coformulated lopinavir/ritonavir-based regimens provide adequate and durable suppression of viral load and sustained improvements in CD4+ cell counts, as demonstrated in randomised trials in antiretroviral therapy-naïve and -experienced adults and children. To date, development of primary resistance to lopinavir/ritonavir has not been observed in 470 antiretroviral therapy-naïve patients treated for >48 weeks. The lopinavir/ritonavir-based regimen was more effective than nelfinavir in antiretroviral therapy-naïve HIV-1-infected patients in a phase III trial. The coformulation is also effective as 'salvage' therapy, as shown by low cross-resistance rates in patients who failed to respond to treatment with other PIs in phase II trials. Coformulated lopinavir/ritonavir was well tolerated in both antiretroviral therapy-naïve and -experienced HIV-1-infected adults and children with low rates of study drug-related treatment discontinuations.*

✓ **Lopinavir-Ritonavir Versus Nelfinavir For The Initial Treatment Of HIV Infection².**

Abstract: *BACKGROUND: Lopinavir is a newly developed inhibitor of human immunodeficiency virus (HIV) protease that, when formulated with ritonavir, yields mean trough plasma lopinavir concentrations that are at least 75 times as high as that needed to inhibit replication of wild-type HIV by 50 percent. METHODS: We conducted a double-blind trial in which 653 HIV-infected adults who had not received antiretroviral therapy for more than 14 days were randomly assigned to receive either lopinavir-ritonavir (400 mg of lopinavir plus 100 mg of ritonavir twice daily) with nelfinavir placebo or nelfinavir (750 mg three times daily) with lopinavir-ritonavir placebo. All patients also received open-label stavudine and lamivudine. The primary efficacy end points were the presence of fewer than 400 HIV RNA copies per milliliter of plasma at week 24 and the time to the loss of virologic response through week 48. RESULTS: At week 48, greater proportions of patients treated with lopinavir-ritonavir than of patients treated with nelfinavir had fewer than 400 copies of HIV RNA per milliliter (75 percent vs. 63 percent, $P < 0.001$) and fewer than 50 copies per milliliter (67 percent vs. 52 percent,*

¹ Risto S. Cvetkovic and Karen L. Goa. *Drugs*. 2003;63(8):769-802.

² Walmsley S, Bernstein B, King M, Arribas J, Beall G, Ruane P, Johnson M, Johnson D, Lalonde R, Japour A, Brun S, Sun E; M98-863 Study Team. *N Engl J Med*. 2002 Jun 27;346(26):2039-46.

150

$P < 0.001$). The time to the loss of virologic response was greater in the lopinavir-ritonavir group than in the nelfinavir group (hazard ratio, 2.0; 95 percent confidence interval, 1.5 to 2.7; $P < 0.001$). The estimated proportion of patients with a persistent virologic response through week 48 was 84 percent for patients receiving lopinavir-ritonavir and 66 percent for those receiving nelfinavir. Both regimens were well tolerated, with the rate of discontinuation related to the study drugs at 3.4 percent among patients receiving lopinavir-ritonavir and 3.7 percent among patients receiving nelfinavir. Among patients with more than 400 copies of HIV RNA per milliliter at some point from week 24 through week 48, resistance mutations in HIV protease were demonstrated in viral isolates from 25 of 76 nelfinavir-treated patients (33 percent) and none of 37 patients treated with lopinavir-ritonavir ($P < 0.001$). **CONCLUSIONS:** For the initial treatment of HIV-infected adults, a combination regimen that includes lopinavir-ritonavir is well tolerated and has antiviral activity superior to that of a nelfinavir-containing regimen.

✓ **Clinical Use Of Lopinavir/Ritonavir In A Salvage Therapy Setting: Pharmacokinetics And Pharmacodynamics³.**

Abstract: Lopinavir/ritonavir was administered to 35 HIV-infected patients after therapeutic failure with other protease inhibitors. The pharmacokinetics (trough concentrations) and baseline viral genotype were determined, together with the immunovirological outcome. The 22 responders had significantly higher mean lopinavir concentrations and lower baseline numbers of mutations. On multivariate analysis, a lopinavir concentration of 5.7 microg/ml or greater was an independent predictor of viral suppression over a 9-month follow-up period.

✓ **Forty-Eight-Week Evaluation Of Lopinavir/Ritonavir, A New Protease Inhibitor, In Human Immunodeficiency Virus-Infected Children.**

Abstract: **BACKGROUND:** Lopinavir/ritonavir has demonstrated antiviral activity in the HIV-infected adult. **SUBJECTS:** The objective of this study was to investigate a liquid coformulation of lopinavir/ritonavir, in combination with reverse transcriptase inhibitors, in HIV-infected children. **METHODS:** One hundred antiretroviral (ARV)-naive and ARV-experienced, nonnucleoside reverse transcriptase inhibitor-naive children between 6 months and 12 years of age participated in this Phase I/II, open label, multicenter trial. Subjects initially received either 230/57.5 mg/m² or 300/75 mg/m² lopinavir/ritonavir twice daily; ARV-naive subjects also received stavudine and lamivudine, whereas ARV-experienced subjects also received nevirapine and one or two nucleoside reverse transcriptase inhibitors. Lopinavir/ritonavir pharmacokinetics, safety and efficacy were evaluated. **RESULTS:** All subjects were escalated to the 300/75 mg/m² twice daily dose based on results from an interim pharmacokinetic and safety evaluation. The pharmacokinetics of lopinavir did not appear to be dependent on age when dosing was based on body surface area but were decreased on coadministration with nevirapine. Overall 79% of subjects had HIV RNA levels <400 copies/ml at Week 48 (intent-to-treat: missing = failure). Mean increases in absolute and relative (percent) CD4 counts from baseline to Week 48 were observed in both ARV-naive subjects (404 cells/mm³; 10.3%) and ARV-experienced subjects (284 cells/mm³; 5.9%). Only one subject prematurely discontinued the study because of a study drug-related adverse event. **CONCLUSIONS:** The liquid coformulation of lopinavir/ritonavir demonstrated durable antiviral activity and was safe and well-tolerated after 48 weeks of treatment in HIV-infected children.

³ Boffito M, Arnaudo I, Raiteri R, Bonora S, Sinicco A, Di Garbo A, Reynolds HE, Hoggard PG, Back DJ, Di Perri G. AIDS. 2002 Oct 18;16(15):2081-3.

13x
14x
15x

✓ **Long-Term Safety And Durable Antiretroviral Activity Of Lopinavir/Ritonavir In Treatment-Naive Patients: 4 Year Follow-Up Study⁴.**

Abstract: *OBJECTIVE:* Combination antiretroviral therapy with lopinavir/ritonavir (LPV/r) has been highly effective in clinical trials. Results of long-term therapy with LPV/r-based regimens have not been previously reported. This study describes the 4-year (204-week) safety and antiretroviral activity of LPV/r-based treatment in antiretroviral-naive individuals. *DESIGN:* Long-term, open-label follow-up of a phase II, prospective, randomized, multicenter trial. *METHODS:* A group of 100 antiretroviral-naive HIV-infected patients were randomized to one of three blinded doses of LPV/r [200/100 mg (n = 16), 400/100 mg (n = 51), or 400/200 mg (n = 33)] with stavudine 40 mg and lamivudine 150 mg every 12 hours. After 48 weeks, LPV/r was dosed open-label at 400/100 mg every 12 hours with stavudine and lamivudine. *RESULTS:* Mean baseline plasma HIV-1 RNA and CD4 cell count were 4.9 log₁₀ copies/ml and 338 x 10 cells/l, respectively. At week 204, 72 patients remained on study, 70 of whom had HIV-1 RNA < 50 copies/ml (70% by intent-to-treat analysis). Twenty-eight patients discontinued therapy prior to week 204 because of adverse events (n = 10), lost to follow-up (n = 9), or other reasons (n = 9). Of 15 patients who met protocol-defined criteria for virologic failure, seven remained on the study regimen and their HIV-1 RNA was re-suppressed to < 50 copies/ml at week 204. Genotypic analysis of rebound viral isolates was available from 10 patients, including all eight patients who discontinued the study prematurely. No isolate demonstrated primary or active site mutations in protease. The most common adverse events were gastrointestinal symptoms and lipid elevations. *CONCLUSIONS:* LPV/r-based therapy provides durable antiretroviral response and is generally well tolerated through 204 weeks of therapy.

Como se puede apreciar, en estas publicaciones la combinación entre lopinavir y ritonavir es una combinación farmacológica ampliamente reconocida y estudiada para el tratamiento de pacientes infectados con VIH. De esta manera la solicitud colombiana en trámite no puede sustentar de ninguna manera nivel inventivo alguno al reivindicar dicha combinación farmacológica en una formulación farmacéutica.

✓ Entre otros documentos que revelan con anterioridad la combinación farmacéutica entre lopinavir y ritonavir, pueden mencionarse la publicación internacional WO 02/096395 publicada el 05 de Diciembre de 2002 y titulada "SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR" la cual revela:

The soft elastic capsule of claim 1 wherein said pharmaceutical agent comprises a solubilized HIV inhibiting compound or a combination of solubilized HIV inhibiting compounds.

⁴ Hicks C, King MS, Gulick RM, White AC Jr, Eron JJ Jr, Kessler HA, Benson C, King KR, Murphy RL, Brun SC. AIDS. 2004 Mar 26;18(5):775-9.

135
150
152

The soft elastic capsule of claim 4 wherein said HIV inhibiting compound is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

The soft elastic capsule of claim 4 wherein said combination of solubilized HIV inhibiting compounds is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane (lopinavir).

✓ Así mismo la publicación internacional WO 2005/007070 publicada el 27 de enero de 2005 y titulada "STABLE PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF HIV PROTEASE INHIBITORS AND PROCESS FOR PREPARING A CONCENTRATE PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF HIV PROTEASE INHIBITORS" revela:

A pharmaceutical composition of claim 1, characterized by comprising a combination between [1S-[1R*, (R*), 3R*, 4R*]]-N-[4-[[(2,3-Dimethylphenoxy) acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl) pentyl]tetrahydro- α -(1-methylethyl)-2-oxo-1-(2H)-pyrimidineacetamide (lopinavir) and [5S-(5R*, 8R*, 10R*, 11R*)]-10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-acid 2,4,7,12-tetraazatridecan-13-oic 5-thiazolylmethyl ester (ritonavir), which are present in a weight ratio ranging from 9:1 to 1:9 respectively, being the combination used in a concentration ranging from 1.0% to 60% in weight of the final composition, more preferably in a concentration ranging from 10% to 50% in weight of the final composition;

126
151
153

con lo que se evidencia nuevamente que dicha combinación farmacológica entre lopinavir y ritonavir, es una combinación ampliamente descrita y utilizada en el estado de la técnica.

➤ Ahora bien, la publicación internacional WO 01/34119 publicada el 17 de Mayo de 2001 y titulada "INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION" revela:

This invention pertains to the preparation of solid dispersion systems for pharmaceuticals which demonstrate a lack of crystallization.

The invention involves dispersion in a hydrophilic matrix of pharmaceuticals which exhibit poor aqueous solubility. The intent of such a formulation is to improve the aqueous dissolution properties and ultimately achieve improved bioavailability. Typically, the intent of such systems is to generate a dispersion of amorphous (high energy) drug within the matrix. The presence of the high energy drug form usually improves the dissolution rate. However, these systems are not often physically stable. The drug can crystallize over time, causing the loss of the desired properties and reduced shelf-life. The current invention enhances the physical stability of such formulations, thereby making this type of formulation more feasible.

In the instant invention, PEG 8000 is used as the hydrophilic matrix. Also employed in this formulation is polyvinylpyrrolidone (PVP), which is an example of a hydrophilic, amorphous polymer, and is used to inhibit crystallization. Other hydrophilic, amorphous polymers

152
154

1. A pharmaceutical composition comprising a solid dispersion of a pharmaceutical compound, a water soluble carrier, and a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone (PVP) and hydroxypropylcellulose (HPMC). (...)

3. The composition of Claim 1 wherein said pharmaceutical compound is an HIV protease inhibitor dissolved in an organic solvent. (...)

5. The composition of Claim 3 wherein said HIV protease inhibitor is 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir). (...)

6. The composition of Claim 3 wherein said HIV protease inhibitor is (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane (ABT-378).

138
133
155

7. The composition of Claim 3 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

(...)

20. A method of treating an HIV infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is an HIV protease inhibitor.

21. The method of Claim 20 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

Esta anterioridad describe formulaciones farmacéuticas que contienen la combinación farmacológica entre ritonavir y lopinavir y su uso en el tratamiento de la infección HIV; además, es importante resaltar que se encuentran en forma de dispersión sólida, y en donde los dos fármacos se encontrarían en forma amorfa debido a la presencia de un inhibidor de la cristalización, en este caso mediante el

empleo de PVP, con lo cual se hace evidente la falta de novedad y de nivel inventivo de lo reivindicado por la solicitud en trámite.

➤ Por ultimo, es relevante resaltar que la solicitud colombiana en trámite no solo carece de novedad y de nivel inventivo como se ha demostrado con los argumentos anteriores, sino que además incurre en una improcedencia directa de patentabilidad dado el hecho que en su capítulo reivindicatorio, específicamente en su reivindicación 14, describe un método terapéutico, lo cual es inaceptable a la luz de la Decisión 486 del año 2000 la cual expone explícitamente en su artículo 20 literal d) que *"No serán patentables (...) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales."*

Por todo lo anterior reitero que la solicitud de la referencia, en todas sus reivindicaciones, incumple los requisitos materiales de patentabilidad establecidos por la Decisión 486 de 2000, razón por la cual no puede ser objeto de privilegio de patente de invención.

VI. ANEXOS

- Abstracts de todas las publicaciones científicas mencionadas en el acápite de Complemento de Información.
- La publicación internacional WO 02/096395 publicada el 05 de Diciembre de 2002 y titulada "SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR" capítulo reivindicatorio.
- La publicación internacional WO 2005/007070 publicada el 27 de enero de 2005 y titulada "STABLE PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF HIV PROTEASE INHIBITORS AND PROCESS FOR PREPARING A CONCENTRATE PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF HIV PROTEASE INHIBITORS" capítulo reivindicatorio.
- La publicación internacional WO 01/34119 publicada el 17 de Mayo de 2001 y titulada "INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION" páginas 10, 14, y capítulo reivindicatorio.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A 44.655 del C.S.J.

10
157

Lopinavir/Ritonavir

A Review of its Use in the Management of HIV Infection

Risto S. Cvetkovic and Karen L. Goa

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

B.G. Gazzard, Chelsea & Westminster Hospital, London, England; *M. Loutfy*, Immune Deficiency Treatment Centre, McGill University Health Centre, Montreal, Quebec, Canada; *M. Markowitz*, Aaron Diamond AIDS Research Center and Rockefeller University, New York, New York, USA; *R.L. Murphy*, Department of Medicine, Division of Infectious Diseases, Northwestern University, Chicago, Illinois, USA; *L. Perrin*, Département de Médecine, Division des Maladies Infectieuses, Laboratoire Central de Virologie, Hôpital Cantonal, Hôpitaux Universitaires de Genève, Geneva, Switzerland; *R.P.G. van Heeswijk*, Division of Infectious Diseases, Clinical Investigation Unit, The Ottawa Hospital, Ottawa, Ontario, Canada; *P. Vernazza*, Department of Medicine, Division of Infectious Diseases, Cantonal Hospital, St Gallen, Switzerland; *S. Walmsley*, Division of Infectious Diseases, Toronto General Hospital, Toronto, Ontario, Canada; *J.B. Ziegler*, Department of Immunology and Infectious Diseases, Sydney Children's Hospital, Sydney, New South Wales, Australia.

Data Selection

Sources: Medical literature published in any language since 1980 on lopinavir/ritonavir, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'lopinavir and ritonavir'. EMBASE search terms were 'lopinavir and ritonavir'. AdisBase search terms were 'lopinavir-ritonavir'. Searches were last updated 7 March 2003.

Selection: Studies in patients with HIV-1 infection who received lopinavir/ritonavir coformulation. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: lopinavir/ritonavir, coformulation, HIV-1, AIDS, adults, children, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary	770
1. Introduction	775
2. Overview of Pharmacodynamic Properties	776
2.1 Mechanism of Action	776
2.2 Antiretroviral Activity	776
2.2.1 <i>In Vitro</i>	776
2.2.2 <i>In Vivo</i>	776
2.3 Resistance	777
2.3.1 In Antiretroviral Therapy-Naïve Patients	777
2.3.2 In Protease Inhibitor (PI)-Experienced, Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Naïve Patients	777
2.3.3 In PI- and NNRTI-Experienced Patients	777
2.3.4 In Children with HIV-1 Infection	778
3. Overview of Pharmacokinetic Properties	778
3.1 Absorption	778
3.1.1 Effects of Food on Oral Absorption	779
3.2 Distribution	779
3.3 Metabolism	779
3.4 Elimination	780
3.5 In Special Patient Populations	780
3.5.1 In Children	780

4. Drug Interactions.....	780
4.1 Drugs Not to Be Coadministered with Lopinavir/Ritonavir	781
4.2 Concomitant Drug Administration Requiring Dosage Adjustment	781
4.2.1 Interactions Between Lopinavir/Ritonavir and Other Antiretroviral Drugs	781
4.2.2 Effect of Lopinavir/Ritonavir on Non-Antiretroviral Drugs	783
4.2.3 Effects of Non-Antiretroviral Drugs on Lopinavir/Ritonavir	784
5. Therapeutic Efficacy	784
5.1 In Adults	784
5.1.1 Antiretroviral Therapy-Naïve Patients	785
5.1.2 Antiretroviral Therapy-Experienced Patients	787
5.2 In Children	790
6. Tolerability.....	790
6.1 In Adults	790
6.1.1 Comparative Trials	790
6.1.2 Noncomparative Trials	792
6.2 In Children	792
7. Pharmacoeconomic Analyses.....	793
8. Dosage and Administration	793
9. Place of Lopinavir/Ritonavir in the Management of HIV Infection	794

Summary

Abstract

Lopinavir is a novel protease inhibitor (PI) developed from ritonavir. Coadministration with low-dose ritonavir significantly improves the pharmacokinetic properties and hence the activity of lopinavir against HIV-1 protease. Coformulated lopinavir/ritonavir was developed for ease of administration and to ensure both drugs are taken together, as part of combination therapy with other antiretroviral agents.

Coformulated lopinavir/ritonavir-based regimens provide adequate and durable suppression of viral load and sustained improvements in CD4⁺ cell counts, as demonstrated in randomised trials in antiretroviral therapy-naïve and -experienced adults and children. To date, development of primary resistance to lopinavir/ritonavir has not been observed in 470 antiretroviral therapy-naïve patients treated for >48 weeks. The lopinavir/ritonavir-based regimen was more effective than nelfinavir in antiretroviral therapy-naïve HIV-1-infected patients in a phase III trial. The coformulation is also effective as 'salvage' therapy, as shown by low cross-resistance rates in patients who failed to respond to treatment with other PIs in phase II trials.

Coformulated lopinavir/ritonavir was well tolerated in both antiretroviral therapy-naïve and -experienced HIV-1-infected adults and children with low rates of study drug-related treatment discontinuations. The most common adverse event in adults associated with lopinavir/ritonavir was diarrhoea, followed by other gastrointestinal disturbances, asthenia, headache and skin rash. The incidence of moderate-to-severe adverse events in children was low, skin rash being the most common. Changes in body fat composition occurred with equal frequency in lopinavir/ritonavir- and nelfinavir-treated naïve patients, through week 60 in a phase III study. Although laboratory abnormalities occurred with similar frequency in both treatment groups, triglycerides grade 3/4 elevations were significantly more frequent with lopinavir/ritonavir. Total cholesterol and triglycerides grade 3/4 elevations appear to occur more frequently in PI-experienced than in PI-naïve lopinavir/ritonavir-treated patients.

A number of clinically important drug interactions have been reported with lopinavir/ritonavir necessitating dosage adjustments of lopinavir/ritonavir and/or the interacting drugs, and several other drugs are contraindicated in patients receiving the coformulation.

13
14
15
16

Conclusion: Coformulated lopinavir/ritonavir is a novel PI that, in combination with other antiretroviral agents, suppresses plasma viral load and enhances immunological status in therapy-naïve and -experienced patients with HIV-1 infection. Lopinavir/ritonavir appears more effective than nelfinavir in 'naïve' patients and is also suitable for 'salvage' therapy, because of its high barrier to development of resistance. Given its clinical efficacy, a tolerability profile in keeping with this class of drugs, favourable resistance profile and easy-to-adhere-to administration regimen, coformulated lopinavir/ritonavir should be regarded as a first-line option when including a PI in the management of HIV-1 infection.

Overview of Pharmacodynamic Properties

Lopinavir/ritonavir is a coformulation of two structurally related protease inhibitor (PI) antiretroviral agents. Lopinavir is a highly potent and selective inhibitor of the HIV type 1 (HIV-1) protease, an essential enzyme for production of mature, infective virus. It acts by arresting maturation of HIV-1 thereby blocking its infectivity. Thus, the main antiviral action of lopinavir is to prevent subsequent infections of susceptible cells; it has no effect on cells with already integrated viral DNA. Lopinavir has an ≈ 10 -fold higher *in vitro* activity against both wild-type and mutant HIV-1 proteases than ritonavir; however, its *in vivo* activity is greatly attenuated by a high first-pass hepatic metabolism. The low-dose ritonavir coadministered with lopinavir inhibits metabolic inactivation of lopinavir and acts only as its pharmacokinetic enhancer. Therefore, the antiretroviral activity of coformulated lopinavir/ritonavir 400/100mg twice daily is derived solely from lopinavir plasma concentrations. Combining lopinavir with low-dose ritonavir produces lopinavir concentrations far exceeding those needed to suppress 50% of *in vitro* and *in vivo* viral replication in CD4+ cells and monocyte/macrophages (main human reservoirs of HIV-1 infection).

Thus far, no resistance to lopinavir has been detected in clinical trials in antiretroviral therapy-naïve patients treated for up to 204 weeks and only 12% of HIV-1 strains from patients in whom prior treatment with multiple PIs have failed, have been observed to develop resistance to coformulated lopinavir/ritonavir. A strong negative correlation was found between the number of PI mutations at baseline and the viral response rates achieved with lopinavir/ritonavir-based regimens in PI-experienced patients, indicating that resistance to lopinavir increases with increasing number of PI mutations and that five PI mutations represent the clinically relevant genotypic breakpoint for lopinavir.

Overview of Pharmacokinetic Properties

The absolute bioavailability of lopinavir coformulated with ritonavir in humans has not yet been established. Multiple-dosage absorption pharmacokinetics of lopinavir/ritonavir 400/100mg twice daily (the mean peak [C_{max}] and trough [C_{trough}] plasma concentrations at steady-state and the 12-hour area under the plasma concentration-time curve [AUC_{12}] of either drug) were stable in antiretroviral therapy-naïve and single PI-experienced adult patients receiving therapy over a 24-week evaluation period. The C_{trough} values of lopinavir, achieved with lopinavir/ritonavir 400/100mg twice daily, were median 84-fold higher than the protein binding-adjusted 50% effective concentration (EC_{50}) of lopinavir against wild-type HIV-1 in antiretroviral therapy-naïve HIV-1-infected patients in a phase II study.

Bioavailability of lopinavir administered in either the capsule or the liquid lopinavir/ritonavir formulation can be increased substantially with concurrent ingestion of food with moderate-to-high fat content. At steady state, lopinavir is ≈ 98 –99% plasma protein bound and the percentage of its unbound (i.e. pharmacologically active) fraction is dependent on total drug plasma concentration. Both lopinavir and ritonavir penetrate poorly into the human genital tracts and the cerebrospinal fluid.

T4
143
150
161

Both agents undergo extensive and rapid first-pass metabolism by hepatic cytochrome P450 (CYP) 3A4 isoenzyme. However, ritonavir also potently inhibits this enzyme and acts as a pharmacokinetic enhancer of lopinavir. The elimination half-life and apparent oral clearance of lopinavir average $\approx 4-6$ hours and $\approx 6-7$ L/h, respectively, with lopinavir/ritonavir 400/100mg twice daily administration. Less than 3% and 20% of the lopinavir dose is excreted unchanged in the urine and faeces, respectively. Limited data show similar pharmacokinetics of lopinavir in children as in adults.

Drug Interactions

Coformulated lopinavir/ritonavir has the potential to interact with wide variety of drugs via several mechanisms, mostly involving the CYP enzymes. Coadministration of lopinavir/ritonavir is contraindicated with certain drugs (i.e. flecainide, propafenone, astemizole, terfenadine, ergot derivatives, cisapride, pimozide, midazolam and triazolam) that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Coadministration with lopinavir/ritonavir is also not recommended for drugs or herbal products (i.e. rifampicin [rifampin] and St. John's wort [*Hypericum perforatum*]) that may substantially reduce lopinavir plasma concentrations, or drugs whose plasma concentrations elevated by the coformulation may lead to serious adverse reactions (i.e. simvastatin and lovastatin). However, a recent study in healthy volunteers suggests that adequate lopinavir concentrations may be achieved during rifampicin coadministration by increasing the twice-daily dosage of lopinavir/ritonavir in conjunction with therapeutic drug monitoring. The liquid (but not the capsule) formulation of lopinavir/ritonavir contains 42.4% ethanol (v/v) and should not be coadministered with drugs capable of producing disulfiram-like reactions (e.g. disulfiram, metronidazole).

Coadministration with saquinavir or indinavir requires no dosage adjustment, whereas coadministration with amprenavir, nevirapine or efavirenz requires a dosage increase of the coformulation typically by 33%. As the oral bioavailability of both didanosine and lopinavir/ritonavir is significantly affected by concurrent food ingestion, didanosine should be administered 1 hour before or 2 hours after lopinavir/ritonavir has been taken with food. Interactions between lopinavir/ritonavir and other nucleoside reverse transcriptase inhibitors (NRTIs) are not expected.

The coformulation is also likely to increase plasma concentrations of non-antiretroviral drugs metabolised through the CYP3A pathway. To reduce the risk of their toxicity when coadministered with lopinavir/ritonavir, the recommended actions include: (i) monitoring of the drug plasma concentration (antiarrhythmics and immunosuppressants) or the international normalised ratio (warfarin); (ii) the use of alternative treatment (atorvastatin) or birth control methods (ethinylestradiol); and (iii) dosage adjustment (clarithromycin [only in patients with renal failure], rifabutin, dihydropyridine calcium-channel blockers, atorvastatin, ketoconazole and itraconazole). Coadministration of lopinavir/ritonavir 400/100mg twice daily significantly reduces the C_{max} and AUC of methadone but does not appear to precipitate opioid withdrawal symptoms or require methadone dosage adjustment and could be useful in treatment of HIV-1-infected patients who are users of illicit intravenous narcotics. Drugs that induce CYP3A-mediated clearance of lopinavir and lower its plasma concentration should be used with caution (corticosteroids) or with dosage adjustment of lopinavir/ritonavir (carbamazepine, phenytoin and barbiturates) when coadministered with it.

No clinically significant interactions were observed during coadministration of norethindrone or pravastatin with lopinavir/ritonavir. Likewise, coadministration of rifabutin or ketoconazole does not require lopinavir/ritonavir dosage

adjustment. Clinically significant interactions are not expected between lopinavir/ritonavir and either fluvastatin, dapsone, cotrimoxazole, azithromycin, erythromycin or fluconazole.

Therapeutic Efficacy

The therapeutic efficacy of lopinavir/ritonavir in combination with other antiretroviral agents has been evaluated in several (both comparative and noncomparative) phase II/III clinical trials in antiretroviral therapy-naïve and -experienced adults and children, and in two large (>11 000 participants) prospective, nonblind, noncomparative 'salvage' programmes in adults with HIV-1 infection. All trials used decreasing plasma HIV-1 RNA levels (viral load) and increasing CD4+ cell counts as surrogate markers of clinical drug efficacy. The effects of lopinavir/ritonavir on HIV-1- and AIDS-related morbidity and mortality are yet to be established.

Lopinavir coformulated with ritonavir in three different dose combinations (200/100mg, 400/100mg and 400/200mg) administered twice daily in combination with standard dosages of the two commonly used NRTIs (lamivudine and stavudine) induced a rapid decline in plasma HIV-1 RNA levels that was sustained throughout the 48-week study period (the mean reduction from baseline was 2.23 log₁₀ copies/mL) in a phase II trial in 100 antiretroviral therapy-naïve patients. In the nonblind extension of this study, lopinavir/ritonavir 400/100mg twice daily produced continued suppression of viral load <50 copies/mL in a substantial proportion of patients (70% and 97% by intent-to-treat and on-treatment analyses), and improved immunological status of patients through week 204 (the mean increase from baseline in CD4+ cell count was 440 cells/ μ L), regardless of patient's baseline immune status.

The efficacy of lopinavir/ritonavir 400/100mg twice daily in combination with lamivudine and stavudine compared favourably with that of a nelfinavir (750mg three times daily)-based PI-triple (a PI plus two NRTIs) regimen in a large randomised, double-blind phase III study in 653 antiretroviral therapy-naïve adults with HIV-1 infection. Lopinavir/ritonavir demonstrated significantly greater suppression of plasma HIV-1 RNA levels than nelfinavir, starting from week 20 (<400 copies/mL) and week 32 (<50 copies/mL) and persisting through weeks 48 and 60. Significantly more patients receiving lopinavir/ritonavir-based triple therapy maintained viral response at both timepoints than recipients of the nelfinavir-based regimen. Both drugs had similar overall effects on patients' immune systems; however, in patients with a very poor immune responsiveness at baseline (CD4+ cell count <50 cells/ μ L), lopinavir/ritonavir induced a significantly greater increase in the mean CD4+ cell count compared with nelfinavir, after 60 weeks of treatment. Lopinavir/ritonavir-based therapy was equally as effective in female as in male patients with HIV-1 infection, with or without hepatitis B and/or C virus (HBV/HCV) co-infection.

In 70 patients experiencing virological failure with treatment regimens comprising a single PI, alone or combined with one or more NRTI, substitution of their prior PI with lopinavir/ritonavir (400/100mg or 400/200mg twice daily) produced rapid (within the first 2 weeks of treatment) viral suppression (viral load <400 copies/mL or ≥ 1 log₁₀ copies/mL reduction from baseline) in 80% of patients and rapid improvement in CD4+ cell count (increase was significant from week 8). These results were maintained at 48 weeks and for the duration of the study in patients who continued lopinavir/ritonavir-based salvage therapy, with no statistically significant differences recorded between the two lopinavir/ritonavir dosage combinations. At week 144, plasma HIV-1 RNA levels were suppressed below 400 copies/mL in at least half and below 50 copies/mL in almost half (49%) of the patients. All patients also received nevirapine and had their baseline

16
14
163

NRTI regimen changed to include at least one NRTI they had not received previously.

A smaller randomised, nonblind phase II trial in multiple PI-experienced but non-nucleoside reverse transcriptase inhibitor (NNRTI)-naive HIV-infected adults ($n = 57$) found two lopinavir/ritonavir dosage combinations (400/100mg vs 533/133mg twice daily) to have similar efficacy at 24 weeks in an antiretroviral regimen containing efavirenz 600mg once daily and NRTIs of the investigators' choice. In the noncomparative extension of the study, treatment with the lopinavir/ritonavir 533/133mg twice-daily regimen maintained a high level of viral load suppression and continued to improve the CD4+ cell count, throughout week 72. Baseline *in vitro* phenotypic and genotypic susceptibility to lopinavir of viral isolates had an important influence on virological response throughout the course of study (see Overview of Pharmacodynamic Properties summary).

The efficacy of lopinavir/ritonavir coformulation has also been evaluated in two large (>11 000 participants in 35 countries worldwide) prospective, nonblind, noncomparative 'salvage' programmes (the Expanded Access Program [EAP] and the ATU programme [Autorisation Temporaire d' Utilisation] in HIV-1-infected adults who had failed to respond to and/or were intolerant to combinations of other available antiretroviral agents. Participants in both studies had significant prior exposure to both PIs and NNRTIs, and a large proportion had advanced disease on enrolment. In both studies patients received lopinavir/ritonavir 400/100mg twice daily with the dosage increase to 533/133mg if concomitant treatment included nevirapine or efavirenz. After the first 24 weeks of treatment with lopinavir/ritonavir-based salvage regimens in the EAP, overall >50% of patients achieved a viral load of ≤ 500 copies/mL, with $\approx 75\%$ of patients attaining at least 1 log₁₀ copies/mL reduction from baseline. In the ATU programme, a similar percentage ($\approx 72\%$) of patients achieved viral response (defined as plasma HIV-1 RNA level <400 copies/mL or ≥ 1 log₁₀ copies/mL decrease from baseline). An association was observed between the baseline lopinavir mutation score and the virological response to lopinavir/ritonavir-based treatment (see Overview of Pharmacodynamic Properties summary).

Data in children are limited to a nonblind, phase I/II study in antiretroviral therapy-naive ($n = 44$) and -experienced ($n = 56$) children (aged between 3 months and 12 years). All patients received regimens based on lopinavir/ritonavir 300/75 mg/m² twice daily (increased from 230/57.5mg twice daily after 3 weeks). After 72 weeks, lopinavir/ritonavir-based regimens adequately suppressed plasma HIV-1 RNA levels in most patients in both groups, although overall responses tended to be lower in experienced patients. Immune status of patients in each group continually improved throughout the study.

Tolerability

Coformulated lopinavir/ritonavir appeared to be well tolerated in both antiretroviral therapy-naive and -experienced HIV-1-infected adults and children, in comparative and noncomparative clinical trials, which was reflected by the low rates of study drug-related discontinuation of therapy (i.e. 4–7% through 60–204 weeks of therapy across the four comparative phase II/III trials in adults and 1% through 72 weeks of therapy in a single trial in children). This rate of discontinuation was unaffected by baseline HBV/HCV status in a phase III study in adults.

The most frequently reported adverse event in adults, of at least moderate severity, was diarrhoea (12–31% incidence) in phase II/III clinical trials and in both antiretroviral therapy-naive and -experienced patients. Other less common complaints included other gastrointestinal disturbances (nausea, abdominal pain, vomiting), asthenia, headache and skin rash. The incidence of adverse events of at least moderate severity in children was low (11% overall); skin rash was the most common occurring in 2%, and allergic reactions, fever, viral infections, constipa-

15
H
X62
164

tion, hepatomegaly, pancreatitis, vomiting, dry skin and taste perversion all occurred in 1% of patients. In the EAP, serious adverse events such as myocardial infarction, pancreatitis, lactic acidosis and hepatic failure were infrequent (<1%) during lopinavir/ritonavir therapy. Adverse events consistent with changes in body fat composition (including lipodystrophy, obesity and abdomen enlargement [2% each] and Cushingoid appearance, multiple lipomas and gynaecomastia [$\leq 1\%$ each]) were observed with equal frequency (7%) in lopinavir/ritonavir- or nelfinavir-treated 'naive' patients, through week 60 in the phase III study.

In the only phase III trial in adults, grade 3/4 laboratory abnormalities occurred with similar frequencies in lopinavir/ritonavir- and nelfinavir-treated 'naive' patients, except for the elevation in triglyceride levels, which occurred more frequently with lopinavir/ritonavir than with nelfinavir (11% vs 2%; $p < 0.001$). The incidence of grade 3/4 elevations in total cholesterol and triglycerides levels appears higher in PI-experienced than in antiretroviral therapy-naïve patients receiving the coformulation, although evidence from direct comparison is still lacking. Biochemical abnormalities of grade 3/4 severity in children were infrequent (<6%).

Pharmacoeconomic Analyses

Thus far, cost consequences of initiating antiretroviral therapy with lopinavir/ritonavir versus nelfinavir as the PI component in the triple regimen (in combination with lamivudine and stavudine) have been estimated in two pharmacoeconomic models. Both models analysed the results from a phase III study (see Therapeutic Efficacy summary) in 625 antiretroviral therapy-naïve HIV-infected patients. Limited data from these analyses estimate a 60-week, 5-year and lifetime cost savings with coformulated lopinavir/ritonavir in comparison with nelfinavir based on higher treatment response rates achieved with the former drug. The estimated incremental cost effectiveness ratio with lopinavir/ritonavir was comparable to values calculated for generic antihypertensive drugs.

Dosage and Administration

Coformulated lopinavir/ritonavir is approved for use in both antiretroviral therapy-naïve and -experienced patients. It is available for oral administration in capsule and liquid formulations. The recommended dosage for adults, in the US, for the treatment of HIV-1 infection is 400/100mg (three capsules or 5mL oral solution) twice daily, and the coformulation should be administered with meals of moderate-to-high fat content in order to improve its oral bioavailability. The drug is indicated for use only in combination with other antiretroviral agents.

A number of clinically important drug interactions have been reported with lopinavir/ritonavir, necessitating dosage adjustments of lopinavir/ritonavir and/or the interacting drugs, and several drugs are contraindicated in patients receiving the coformulation (see Drug Interactions summary). Lopinavir/ritonavir is classified under pregnancy category C in the US. It should be administered with caution in patients with hepatic impairment and with haemophilia A and B.

1. Introduction

In the absence of a cure for HIV infection, the goals of antiretroviral therapy should be to improve patient survival and quality of life, reduce HIV-related morbidity, and restore and/or preserve immunological function through maximal and durable suppression of HIV replication.^[1] In order to achieve these goals, current treatment guidelines strongly recommend the use of triple-drug regimens

comprising a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) as a first-line option for the initial treatment of early and advanced disease.^[1]

Lopinavir is a novel PI developed from, and structurally related to, ritonavir and with the same mechanism of action. The poor oral bioavailability of lopinavir coupled with its extensive and rapid metabolism in the liver, resulting in a short elimina-

tion half-life ($t_{1/2}$), precludes its use as a single PI agent in antiretroviral regimens. However, coadministration with subtherapeutic doses of ritonavir improves these pharmacokinetic properties of lopinavir allowing the drug to exert its highly potent antiretroviral activity.^[2-4]

The pharmacology and therapeutic use of coformulated lopinavir/ritonavir (KaletraTM) has been briefly reviewed previously in *Drugs*.^[5] The current review provides an update on the therapeutic efficacy and tolerability of coformulated lopinavir/ritonavir and its use in the management of HIV-1 infection. An overview of the pharmacodynamic and pharmacokinetic properties of lopinavir/ritonavir, including viral resistance and drug interactions, respectively, is also provided.

2. Overview of Pharmacodynamic Properties

Lopinavir/ritonavir is a coformulation of two structurally related PI antiretroviral agents. The pharmacodynamic properties of lopinavir, the therapeutically active antiviral component of the coformulation, have been briefly reviewed previously.^[5] This section provides a detailed overview of those properties.

2.1 Mechanism of Action

Lopinavir is a highly potent,^[2] peptidomimetic^[6] inhibitor of HIV-1 protease. A hydroxyethylene (instead of peptidic) bond within the molecule makes this drug a nonhydrolysable substrate for HIV-1 protease.^[6,7] This enzyme is a homodimeric aspartic protease involved in the post-translational processing of viral *gag* and *gag-pol* polyprotein products into functional core proteins and viral enzymes.^[6,8] This process, which occurs simultaneously with or immediately after the budding of the (immature) virion from the surface of an infected cell, is essential for the production of mature, infectious viral particles.^[9]

HIV PIs, including lopinavir, prevent cleavage of *gag* and *gag-pol* protein precursors in acutely and chronically infected cells, arresting maturation and thereby blocking the infectivity of nascent virions.^[10,11] The main antiviral action of HIV PIs is, thus, to prevent subsequent infection of susceptible

cells; they have no effect on cells already harbouring integrated proviral DNA.

2.2 Antiretroviral Activity

2.2.1 *In Vitro*

Lopinavir has high specificity for HIV-1 protease, which it inhibits *in vitro* in both T-helper lymphocytes and cells of monocyte-macrophage lineage (two major cellular reservoirs for HIV-1 in infected individuals).^[2] It has greatly improved (≈ 10 -fold) *in vitro* antiretroviral activity and significantly higher binding affinity for both wild-type (≈ 8 -fold) and mutant (≈ 25 - to 140-fold) HIV-1 proteases compared with ritonavir.^[2]

Lopinavir 0.5 nmol/L inhibited 93% of wild-type HIV-1 protease activity *in vitro* and demonstrated $\geq 10^5$ -fold higher specificity for this retroviral enzyme than for the mammalian aspartic proteases renin and cathepsin D and E.^[2] Its *in vitro* activity against both wild-type and V82-mutant HIV-1 proteases in MT4 cells was ≈ 10 -fold greater than that of ritonavir; the mean 50% effective concentrations (EC_{50}) of lopinavir and ritonavir against wild-type HIV-1 were 102 and 1 044 nmol/L, respectively, in a medium containing 50% human serum.^[2] Lopinavir was also active against primary HIV-1 isolates cultured in peripheral blood mononuclear cells, with an EC_{50} of 6.5 nmol/L in the absence of 50% human serum.^[2]

Both lopinavir and ritonavir exhibit high plasma protein binding that can attenuate their therapeutic efficacy (section 3.2). However, the *in vitro* anti-HIV-1 activity of lopinavir is ≈ 4 -fold less affected by plasma protein binding than is the activity of ritonavir.^[12] EC_{50} values for ritonavir against HIV-1 in the presence of 50% human serum were 20- to 30-fold higher than those observed in the absence of serum; in contrast, EC_{50} values for lopinavir increased by only 5- to 8-fold.^[13]

2.2.2 *In Vivo*

The *in vivo* activity of lopinavir is attenuated by a high first-pass hepatic metabolism (section 3.3). Coadministration of low-dose ritonavir with lopinavir inhibits metabolic inactivation of lopinavir and acts only as its pharmacokinetic enhancer. Combining lopinavir with low-dose ritonavir produces thera-

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

1498
164
166

peutic lopinavir concentrations exceeding those needed to inhibit HIV-1 activity *in vivo*.^[2-4]

After a single 400mg oral dose in healthy volunteers, the peak lopinavir plasma concentrations (C_{max}) only briefly exceeded 0.1 mg/L (EC_{50} of lopinavir against wild-type HIV-1 *in vitro*).^[2] However, coadministration of a single 50mg dose of ritonavir increased the lopinavir C_{max} to 5.5 mg/L and produced a 77-fold increase in 24-hour area under the plasma concentration-time curve (AUC).^[2]

Mean steady-state trough lopinavir plasma concentrations (C_{trough}) with lopinavir/ritonavir 400/100mg twice-daily were 53- to 103-fold higher than the protein binding-adjusted EC_{50} of lopinavir against wild-type HIV-1 (0.07 mg/L) in antiretroviral therapy-naïve HIV-1-infected patients ($n = 45$),^[3] and exceeded the EC_{50} for all viral isolates phenotypically tested at baseline in single PI-experienced patients ($n = 7$).^[4] The steady-state C_{max} of ritonavir in these trials (section 3.1) was <7% of that achieved with administration of therapeutic dosage of ritonavir in a single-PI regimen (i.e. 600mg twice daily)^[14] and is below the EC_{50} against wild-type HIV-1 for this drug. Therefore, the antiretroviral activity of coformulated lopinavir/ritonavir 400/100mg twice daily is derived solely from lopinavir plasma concentrations.^[15]

2.3 Resistance

There appears to be a lack of resistance development to lopinavir when coformulated with ritonavir in previously untreated patients (section 2.3.1). Thus far, cross-resistance to coformulated lopinavir/ritonavir has been observed to develop in 12% of HIV-1 strains in NNRTI-naïve patients in whom prior treatment with multiple PIs had failed.^[16] Not surprisingly, lopinavir/ritonavir has shown good therapeutic efficacy in 'salvage' antiretroviral regimens (section 5.1.2) owing to its apparently high barrier to development of resistance.

2.3.1 In Antiretroviral Therapy-Naïve Patients

Thus far, no mutations associated with PI resistance have been detected in viral isolates from antiretroviral therapy-naïve adult patients receiving lopinavir/ritonavir 400/100mg twice daily. Six (of 100)^[17] and 51 (of 326)^[18] patients with sustained viral load rebound (plasma HIV-1 RNA level >400 copies/mL), for whom genotype and phenotype data were available, were analysed up to weeks

204^[17] and 96,^[18] respectively (section 5.1.1 and table V). No mutations indicating PI resistance were found in the isolates from these patients.^[17,18] In contrast, viral isolates from 50% (3 of 6)^[17] and 37% (19 of 51)^[18] of these patients demonstrated resistance to lamivudine.

2.3.2 In Protease Inhibitor (PI)-Experienced, Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Naïve Patients

In 57 multiple PI-experienced but NNRTI-naïve HIV-infected patients (section 5.1.2), viral response to lopinavir/ritonavir-based antiretroviral regimens was influenced by baseline phenotype and genotype of viral isolates.^[19-21] *In vitro* phenotypic susceptibility to lopinavir of the HIV-1 isolates obtained from study participants at baseline was 0.5-96 (median 16.2) times higher than the value of IC_{50} for wild-type HIV-1.^[22] In 24 of 56 (43%) evaluable patients, the baseline viral isolates had ≥ 10 -fold higher IC_{50} for lopinavir relative to wild-type virus.^[20,21] Antiretroviral response rates at week 72 were highest among patients with baseline viral isolates displaying <10-fold reduction of *in vitro* susceptibility towards lopinavir compared with wild-type HIV-1 (93% and 89% response rate at <400 and <50 copies/mL) and, similarly, in patients with baseline viral isolates containing five or less protease mutations that were associated with reduced *in vitro* susceptibility to lopinavir (91% and 87% response rates at <400 and <50 copies/mL).^[20,21] The response rates were lowest in patients with >40-fold reduced susceptibility to lopinavir and eight or more associated protease mutations at baseline (25% and 33% of patients had viral loads <400 and <50 copies/mL, respectively, for both parameters observed).^[20,21] A statistically significant association was found between virological response to lopinavir/ritonavir-based treatment (at ≤ 400 and ≤ 50 copies/mL) and baseline phenotypic ($p \leq 0.001$) and genotypic ($p \leq 0.022$) susceptibility to lopinavir of HIV-1 isolates.^[21]

2.3.3 In PI- and NNRTI-Experienced Patients

Similarly, interim results from 78 PI- and NNRTI-experienced patients from the Spanish Expanded Access Program (EAP; also referred to as the Early Access Program)^[23] and from a subgroup of 179 PI- and NNRTI-experienced patients with baseline HIV-1 protease sequence analysis from the ATU programme (Autorisation Temporaire d'Utilisation)^[24] [section 5.1.2] found strong negative corre-

lation between the number of PI mutations present at baseline and the viral response rates achieved at 6 months with lopinavir/ritonavir-based antiretroviral regimens. Patients harbouring HIV-1 RNA with five or less PI mutations at baseline had better viral response than patients with more than five PI mutations (83% and 88% vs 48% and 51%; $p < 0.001$).^[23,24] Substitutions at codons 71 and 82 were the only mutations in the viral genome independently associated with a lower viral response to lopinavir/ritonavir in the Spanish EAP ($p = 0.04$ and 0.053 , respectively),^[23] whereas in an overall analysis of 793 patients from the ATU programme such mutations were found at positions 10, 20, 36, 46, 54 and 82 (all $p < 0.01$ vs baseline genotype).^[25]

The results from these lopinavir/ritonavir trials in PI-experienced patients indicate that resistance to lopinavir is proportional to the number of PI mutations and that five PI mutations could represent the point at which clinically relevant reduction in lopinavir sensitivity begins to occur.^[20,23,24]

2.3.4 In Children with HIV-1 Infection

Data regarding resistance to coformulated lopinavir/ritonavir in children are limited. Among 20 PI- and NNRTI-experienced HIV-1-infected children with available baseline phenotypes in a phase I/II study (section 5.2 and table VIII), 33% (1 of 3 patients) with >10 -fold and 59% (10 of 17 patients) with <10 -fold reduced baseline susceptibility to lopinavir had <400 copies/mL of HIV-1 RNA in plasma at week 72.^[26]

3. Overview of Pharmacokinetic Properties

The pharmacokinetic properties of lopinavir coadministered with ritonavir have been evaluated in single- (400/50mg^[21] and 400/100mg^[14]) and multiple-dose^[4,27-30] studies in healthy adult volunteers ($n = 75$,^[27] 54^[14] and 14^[2]) and in HIV-1-infected adults who were antiretroviral therapy-naïve ($n = 46$,^[4] and 38^[28-30]) or had prior experience with a single PI drug ($n = 12$).^[4] Except in one pilot study,^[2] lopinavir and ritonavir were administered coformulated in capsules^[4,27-30] or in oral solution.^[14] In multiple-dose studies, the coformulation was administered in once-^[27-30] or twice-daily^[4,27-30] regimens, with food^[28-30] or without regard to food intake.^[4,27] Antiretroviral therapy-naïve and single PI-experienced patients also received standard doses of stavudine and lamivudine, and nevirapine and

two NRTIs, respectively, in addition to lopinavir/ritonavir in two multiple-dose studies.^[4] Some data are extracted from the manufacturer's prescribing information.^[15]

The previous review in *Drugs*^[5] gave an insight into the pharmacokinetic profile of lopinavir. This section provides an overview of the pharmacokinetic properties of lopinavir when coformulated with low-dose ritonavir.

3.1 Absorption

The absolute bioavailability of lopinavir coformulated with ritonavir in humans has not yet been established.^[15] The calculated oral bioavailability of lopinavir (without coadministration of ritonavir) in rats is low (25%).^[2]

Combining lopinavir with low-dose ritonavir produces therapeutic lopinavir concentrations exceeding those needed to inhibit HIV-1 activity *in vivo* (section 2.2.2). After a single oral 400mg dose of lopinavir in healthy volunteers ($n = 14$), plasma concentrations only briefly exceeded the EC₅₀ (0.1 mg/L) and declined to >10 -fold lower values by 8 hours. Coadministration of a single 50mg dose of ritonavir, however, produced sustained elevation of lopinavir C_{max} above EC₅₀ reaching 5.5 mg/L. Likewise, the AUC of lopinavir was increased 77-fold from 0–24 hours by coadministration of low-dose ritonavir.^[2]

Multiple-dosage absorption pharmacokinetics of lopinavir/ritonavir 400/100mg twice daily ($n = 19$) and 800/200mg once daily ($n = 17$) in antiretroviral therapy-naïve patients are summarised in table I.^[28,30] The C_{trough} and inhibitory quotient values (IQ; defined as the ratio between the C_{trough} and the protein-binding-adjusted EC₅₀^[31] or the concentration required to inhibit 50% of viral activity [IC₅₀]^[32] for wild-type HIV-1) from weeks 3 to 48 were lower and more variable in the once-daily compared with the twice-daily regimen ($p < 0.01$).^[28-30] The IQ for the twice-daily regimen ranged from 36 to 174 (median 84).^[28,29]

In another study, the multiple-dosage absorption pharmacokinetics of both lopinavir and ritonavir in the 400/100mg twice-daily regimen were stable over a 24-week evaluation period; values for the C_{max}, C_{trough} and AUC₁₂ for either drug were similar within the 'naïve' ($n = 18$) and the 'experienced' ($n = 7$) patient population over weeks 3–24.^[4] There was a strong positive linear correlation between the

Table 1. Absorption pharmacokinetics of oral lopinavir/ritonavir coformulated as a capsule in adults with HIV-1 infection. Preliminary 48-week results from an ongoing, randomised, pilot study in antiretroviral therapy-naïve patients receiving lopinavir/ritonavir 400/100mg bid (n = 19) or 800/200mg od (n = 17)^a with food^[28,29]

Lopinavir/ritonavir dosage	Lopinavir				Ritonavir			
	C _{max} (mg/L)	C _{trough} (mg/L)	t _{max} (h)	AUC ₂₄ (mg • h/L)	C _{max} (mg/L)	C _{trough} (mg/L)	t _{max} (h)	AUC ₂₄ (mg • h/L)
400/100mg bid	9.8	7.1	4.4	185.2 ^b	0.7	0.3	4.3	9.2 ^b
800/200mg od	10.9	3.6*	6.6*	164.9	0.9*	0.09*	7.3*	8.8

a Patients were also receiving lamivudine 150mg and stavudine 30 or 40mg twice daily.

b Estimated by investigators as 2 x AUC₁₂.

AUC₁₂₍₂₄₎ = area under the drug plasma concentration-time curve during 12 (24)-hour administration period; **bid** = twice daily; C_{max} = peak plasma drug concentration; C_{trough} = trough plasma drug concentration at steady-state; **od** = once daily; t_{max} = time to reach C_{max} following drug administration; * p < 0.05 between treatment regimens.

C_{trough}, C_{max} and AUC of lopinavir and ritonavir for the 400/100mg regimen of the coformulated drug (r = 0.74, 0.64 and 0.61, for the respective parameters; all p < 0.001).^[4]

3.1.1 Effects of Food on Oral Absorption

The bioavailability of lopinavir administered in either the capsule or the liquid lopinavir/ritonavir formulation can be increased substantially with concurrent ingestion of food with moderate-to-high fat content. Therefore, it is recommended that lopinavir/ritonavir be administered with moderate-to-high-fat content meals.^[14,15] The apparent effect is greater for the liquid than for the soft elastic capsule formulation (figure 1).

3.2 Distribution

At steady state, lopinavir is highly bound to both albumin and α_1 -acid glycoprotein, with higher affinity for the latter.^[15] In previous studies in both healthy volunteers and HIV-1-infected adults, plasma protein binding of lopinavir ranged from 98.2% to 99.2% and did not appear to be concentration dependent within the therapeutic range.^[4,27] However, in a recent study in 15 HIV-infected patients the percentage of unbound lopinavir was proportional to the total drug plasma concentration (p = 0.027, r = 0.57, linear regression analysis) and was ~60% higher 2 hours, compared with 12 hours, after lopinavir/ritonavir administration.^[33]

High plasma protein binding is thought to be a likely explanation for undetectable lopinavir levels in the cerebrospinal fluid (CSF) of all (n = 12) adult patients with HIV-1 infection receiving lopinavir/ritonavir 400/100mg twice daily in combination with two NRTIs after 6 months of treatment.^[34]

Direct measurements of drug concentrations taken on two separate occasions in plasma and

cervicovaginal secretions of HIV-1-infected women (n = 5^[35] and 17^[36]) receiving lopinavir/ritonavir (dosage not specified) have shown poor penetration of lopinavir and ritonavir into the female genital tract ($\leq 10\%$ ^[35] and $< 4\%$ ^[36] of their respective plasma concentrations 12 hours after drug administration). In comparison, cervicovaginal concentrations of indinavir, nevirapine and delavirdine were 282–290%, 133% and ~50% of their respective plasma concentrations at the same timepoint.^[35,36]

Similar observations were recently made about penetration of lopinavir into the male genital tract. Penetration of lopinavir into the seminal plasma was very limited in 14 men with HIV-1 infection receiving a lopinavir-containing regimen (dosage not specified) for 4–41 weeks (a median of 16 weeks). All but one patient had seminal plasma concentrations of < 0.5 mg/L (estimated from a graph) and none had concentrations > 5.0 mg/L (the desired therapeutic concentration).^[37,38] Another study reported a median lopinavir concentration ratio in semen and plasma of 7%, but with a large inter-individual variability in the level of lopinavir penetration into semen (0.08–2.35 mg/L; median 0.17 mg/L) in seven men with HIV-1 infection receiving lopinavir/ritonavir 400/100mg twice daily for 6 months in combination with two NRTIs.^[34]

3.3 Metabolism

Studies in human hepatic microsome preparations indicate that both lopinavir and ritonavir undergo extensive and rapid first-pass oxidative metabolism in the liver.^[39,40] Enzymatic inactivation of lopinavir in the liver is mediated by the cytochrome P450 (CYP) 3A4 isoenzyme, while that of ritonavir is carried out by both CYP3A and CYP2D6.^[39,40] Ritonavir is also a highly potent inhibitor of

CYP3A-mediated metabolic reactions.^[41] Thus, co-administration of ritonavir, even in the subtherapeutic dosage range, can significantly enhance the pharmacokinetic properties of lopinavir (section 3.1). In contrast, the concentration of ritonavir required to inhibit the metabolism of saquinavir in human liver microsomes is 3.4-fold higher than that needed to inhibit the metabolism of lopinavir.^[2,42]

3.4 Elimination

The mean $t_{1/2}$ and apparent oral clearance of lopinavir were 4.1–5.8 hours and 6.0–7.1 L/h, respectively, during 24-week trials with lopinavir/ritonavir 400/100mg twice-daily administration in antiretroviral therapy-naïve or -experienced patients.^[4] After

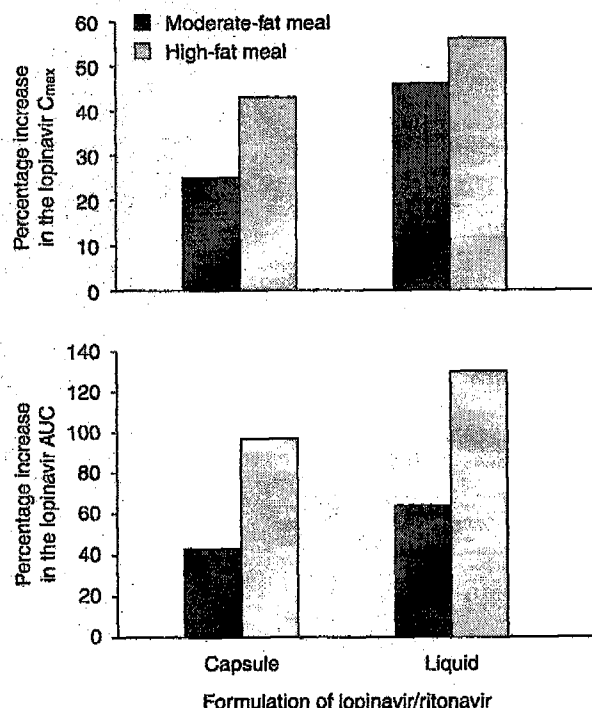


Fig. 1. The effect of food on oral absorption of lopinavir. Data for the lopinavir peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) are from a randomised, nonblind, partial crossover pharmacokinetic study in 54 healthy adult volunteers^[14,15] who received single doses of lopinavir 400mg coformulated with ritonavir 100mg in soft elastic capsule and liquid formulations in a fasting and in two nonfasting regimens (i.e. moderate-fat; 500–682 kcal; 23–25% of calories derived from fat^[15] and high-fat; 872 kcal; 56% from fat^[15]). In the fasting regimen doses were administered after 10-hour fast and 4 hours before lunch, while in nonfasting regimens breakfast was served 30 minutes before dose administration. All results presented are statistically significantly different from the results under fasting conditions ($p < 0.05$ for all comparisons).

a single administration of the same dose of ^{14}C -labelled lopinavir/ritonavir, $\approx 10.4\%$ and 82.6% of ^{14}C -lopinavir was retrieved in the urine and faeces after 8 days. Approximately 2.2% and 19.8% of lopinavir was recovered unchanged in the urine and faeces. After administration of multiple doses of lopinavir/ritonavir, $<3\%$ of the lopinavir dose is excreted unchanged in the urine.^[15]

3.5 In Special Patient Populations

Thus far, pharmacokinetics of lopinavir have not been studied in elderly patients, nor in patients with hepatic insufficiency.^[15] Sex- and race-related differences in pharmacokinetic properties of lopinavir have not been observed in adult patients.^[15] A single case report in an HIV-1-infected patient with renal insufficiency indicated that haemodialysis had no influence on the pharmacokinetics of lopinavir.^[43]

3.5.1 In Children

The pharmacokinetics of lopinavir/ritonavir liquid formulation have been investigated in 53 children (aged between 6 months and 12 years) with HIV-1 infection (see section 5.2 for study details). During a 3-week trial, the 230/57.5 mg/m² twice-daily lopinavir/ritonavir regimen without nevirapine and the 300/75 mg/m² twice-daily regimen with nevirapine produced similar lopinavir plasma concentrations to those achieved in HIV-1-infected adults receiving the lopinavir/ritonavir 400/100mg twice-daily regimen.^[15]

At steady state, lopinavir AUC, C_{max} and C_{trough} for these two paediatric regimens were 72.6 and 85.8 mg $\cdot$ h/L, 8.2 and 10.0 mg/L, and 3.4 and 3.6 mg/L, respectively.^[15]

4. Drug Interactions

Lopinavir and ritonavir are both metabolised through CYP pathways (section 3.3) and therefore have the potential for interactions with a wide variety of drugs.^[44] In addition to being a substrate for hepatic CYP3A4 (section 4.2.3), coformulated lopinavir/ritonavir acts as both a strong inducer and inhibitor of this enzyme (section 4.1 and 4.2.2) and as an inhibitor of CYP2D6 isoenzyme. Ritonavir also increases the biotransformation of some drugs metabolised by glucuronidation (section 4.2.2).

Pharmacokinetic and pharmacodynamic interactions between lopinavir/ritonavir and other drugs have been investigated in trials in small numbers of

HIV-1-infected patients^[45] or healthy volunteers.^[15,46-48] Some information is available only from the manufacturer's prescribing information.^[15] The majority of these studies evaluated only two-drug regimens and their results may not necessarily be applicable to the multidrug regimens often used in clinical practice. This is especially true for regimens comprising three or more drugs with opposing effects on CYP3A4-mediated metabolism, where multidrug interactions may be difficult to predict, thus warranting even closer monitoring for adverse events and/or treatment failure.

4.1 Drugs Not to Be Coadministered with Lopinavir/Ritonavir

According to the manufacturer's prescribing information, coadministration of lopinavir/ritonavir is contraindicated with certain drugs that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (table II).^[15] In contrast, a recent study in healthy volunteers ($n = 15$) indicates that the activity of CYP2D6 is not affected by clinically relevant concentrations of lopinavir/ritonavir.^[48]

Lopinavir/ritonavir may elevate plasma concentrations of the lipid-lowering drugs simvastatin or lovastatin, potentially leading to serious adverse reactions (e.g. myopathy including rhabdomyolysis). Hence, their coadministration with lopinavir/ritonavir is not recommended.^[15] As an alternative, atorvastatin (section 4.2.2) or pravastatin may be used.

Table II. Drugs contraindicated for use with lopinavir/ritonavir^[15]

Drug class (drug name)	Potential clinical effect
Antiarrhythmics (flecainide, propafenone)	Cardiac arrhythmias
Antihistamines (astemizole, terfenadine ^a)	Cardiac arrhythmias
GI motility agent (cisapride ^a)	Cardiac arrhythmias
Neuroleptic (pimozide)	Cardiac arrhythmias
Ergot derivatives (ergonovine, methylergonovine, ergotamine, dihydroergotamine)	Acute ergot toxicity (i.e. peripheral vasospasm and ischaemia of the extremities and other tissues)
Sedative/hypnotics (midazolam, triazolam)	Prolonged or increased sedation, respiratory depression

^a No longer available in the US.

GI = gastrointestinal.

Concomitant use of lopinavir/ritonavir with the antimycobacterial agent rifampicin (rifampin), at standard dosages, or the herbal product St. John's wort (*Hypericum perforatum*) is also not recommended as both drugs may substantially reduce lopinavir plasma concentrations (through induction of lopinavir/ritonavir metabolism), leading to loss of virological response and possible development of resistance to lopinavir/ritonavir or other PI agents.^[15,46,47] However, a recent study in healthy adult volunteers ($n = 32$) indicated that increasing the dosage of lopinavir/ritonavir (i.e. to 400/400mg and possibly 800/200mg, twice daily) in conjunction with therapeutic drug monitoring may allow for concurrent use of rifampicin 600mg once daily in the treatment of tuberculosis in patients with HIV-1 infection.^[49] These results are encouraging, although further studies addressing drug tolerability at these dosages will be necessary.

The liquid formulation of lopinavir/ritonavir contains 42.4% ethanol (v/v)^[15] and should not be coadministered with drugs, such as disulfiram or metronidazole, capable of producing disulfiram-like reactions (i.e. nausea, vomiting, flushing, tachypnoea, tachycardia). The capsule formulation does not contain alcohol.^[15]

4.2 Concomitant Drug Administration Requiring Dosage Adjustment

4.2.1 Interactions Between Lopinavir/Ritonavir and Other Antiretroviral Drugs

Successful antiretroviral therapy requires a combination of at least two and preferably three or more drugs from different classes (i.e. with different mechanisms of action).^[50,51] Coadministration of lopinavir/ritonavir with other antiretroviral drugs may result in clinically relevant pharmacokinetic drug interactions. Table III summarises the effects on absorption pharmacokinetics (C_{max} , C_{trough} , and AUC) of coadministered antiretroviral drugs on lopinavir and/or vice versa in adults (either patients with HIV infection or healthy volunteers).

Interactions with PIs

All PIs are extensively metabolised by CYP enzymes (particularly the CYP3A4 isoenzyme) and drug interactions within this drug class (see table III for details) occur primarily as a result of induction or inhibition of this enzyme.^[61]

As the C_{max} , C_{trough} and AUC of lopinavir are decreased (table III) during coadministration with

Table III. Summary of absorption pharmacokinetic drug interactions between lopinavir/ritonavir (LPV/r) 400/100mg twice daily (bid) and other antiretroviral drugs in adults

Coadministered drug regimen (mg) [duration (days)]	No. of participants (type)	Effect of coadministered drug on LPV pharmacokinetics (% change)			Effect of LPV/r on coadministered drug pharmacokinetics (% change)		
		C _{max}	C _{trough}	AUC	C _{max}	C _{trough}	AUC
In combination with other protease inhibitors							
Amprenavir 750 bid [10] ^[52]	12 (vol)	↓27 ^a	↓49 ^a	↓37 ^a	↑ 9 ^a	↑5.8-fold ^a	↑1.7-fold ^a
Indinavir 600 bid [10] ^[53]	13 (vol)	↑18 ^b	↓ 6 ^b		↓31 ^{ac}	↑2.9-fold ^{ac}	↓14 ^c
Saquinavir 800 bid [10] ^[53]	14 (vol)	↑13 ^b	0 ^b		↑6.2-fold ^{ad}	↑16-fold ^{ad}	↑9.4-fold ^{ad}
Saquinavir 1200 bid [10] ^[53]	10 (vol)	↑ 5 ^b	↓ 8 ^b		↑6.1-fold ^{ad}	↑13-fold ^{ad}	↑8.7-fold ^{ad}
In combination with non-nucleoside reverse transcriptase inhibitors							
Efavirenz 600 qhs [9] ^[55]	11 (vol)	↓ 3	↓28	↓19	↓ 9	↓16	↓16
Efavirenz 600 qhs [14] ^[55]	24 (pts)	↓15 ^e	↓31 ^e	↓25 ^e			
Efavirenz 600 od [35] ^[20,56]	57 (pts)		↓33 ^e	↓25 ^e			
Nevirapine 200 od [14] followed by nevirapine 200 bid [6] ^[57]	5 (vol)	↓ 5	↑ 2	↓ 1	↑ 5	↑15	↑ 9
Nevirapine 200 bid ^[58]	22 (pts)	↓19 ^b	↓46 ^{ab}	↓27 ^{ab}			
In combination with a nucleotide reverse transcriptase inhibitor							
Tenofovir disoproxil fumarate 300 od [14] ^[59,60]	24 (vol)	↓15†	↓10	↓15†	↑31†		↑34†

a Compared with amprenavir values in 11 vol receiving amprenavir 1200mg bid for 15d.

b Compared with historical data in 19 pts receiving LPV/r 400/100mg bid for 21d.^[54]

c Compared with indinavir values in 13 vol receiving indinavir 800mg tid for 5d.

d Compared with saquinavir values in 14 vol receiving saquinavir 1200mg tid for 5d.

e Compared with historical controls receiving LPV/r 400/100mg bid alone.

f Pts were also receiving nucleoside reverse transcriptase inhibitors. Steady-state pharmacokinetic values are reported.

AUC = area under the drug plasma concentration-time curve; C_{max} = peak plasma drug concentration; C_{trough} = trough plasma drug concentration; od = once daily; pts = patients with HIV-1 infection; qhs = once daily at bedtime; tid = three times daily; vol = healthy volunteers; ↓ indicates decrease; ↑ indicates increase; * p < 0.05 vs comparator regimen; † statistical significance established at 90% CI.

amprenavir, the dosage of lopinavir/ritonavir should be increased typically by 33% (i.e. to 533/133mg twice daily in adults), particularly in patients with extensive PI experience or with reduced viral susceptibility to lopinavir.^[52] In contrast, from comparisons with historical data,^[54] the pharmacokinetics of lopinavir (table III) and ritonavir appear to be only minimally affected by coadministration of saquinavir and indinavir requiring no dosage adjustment of lopinavir/ritonavir.

Lopinavir/ritonavir 400/100mg twice daily significantly enhanced absorption pharmacokinetics of saquinavir administered in the 800mg twice-daily regimen (table III), resulting in ≈19-fold increase in the median IQ of saquinavir (compared with results with saquinavir 1200mg three-times-daily regimen).^[53] An increase in the saquinavir dosage from 800 to 1200mg twice daily was, however, not associated with an expected increase in saquinavir ab-

sorption pharmacokinetics, suggesting a plateau effect with the lower-dose regimen.

Coadministration of lopinavir/ritonavir 400/100mg and indinavir 600mg twice daily resulted in a statistically significant decrease in the indinavir C_{max} and an increase in C_{trough} (compared with results with indinavir 800mg three times daily) [table III] and increased the median IQ of indinavir from 4.3 to 11.^[53] Thus, the *in vitro* antiretroviral activity of indinavir, like that of saquinavir, is increased allowing for reduction in dosage and frequency of administration when indinavir, or saquinavir, is coadministered with lopinavir/ritonavir (table III). Appropriate dosages of indinavir, saquinavir and amprenavir when administered in combination with lopinavir/ritonavir have not yet been established (see section 8).

Interactions with NNRTIs

Pharmacokinetic interactions between lopinavir/ritonavir and nevirapine or efavirenz are related to

their common metabolic pathways; both NNRTIs are metabolised by CYP3A (like lopinavir and ritonavir) and to a lesser extent by CYP2D6 (like ritonavir), and they both act as potent CYP3A enzyme inducers (like ritonavir).^[57,58,62] Despite some conflicting results with nevirapine regarding a lack of interaction in healthy volunteers (table III), coadministration of either of these two NNRTIs with lopinavir/ritonavir generally results in statistically significantly decreased lopinavir plasma concentrations (table III). Consequently, a 33% increase in lopinavir/ritonavir dosage is recommended when the coformulation is coadministered with either nevirapine or efavirenz to achieve therapeutic lopinavir plasma concentrations,^[15,55,58,62] although the clinical relevance of pharmacokinetic interactions between nevirapine and lopinavir/ritonavir has not been definitely established.^[58]

Dosage adjustment of efavirenz or nevirapine is not required when coadministered with lopinavir/ritonavir, as the latter drug only marginally alters the C_{max} , C_{trough} and AUC of these NNRTIs, as shown in healthy volunteers (table III).^[55,57]

Interactions with Nucleoside or Nucleotide Reverse Transcriptase Inhibitors

Lopinavir/ritonavir is also commonly prescribed in combination with NRTIs. However, pharmacokinetic drug interactions are unlikely as their metabolic pathways do not involve the CYP enzymes

responsible for inactivation of lopinavir/ritonavir. Whether lopinavir/ritonavir interferes with intracellular phosphorylation of NRTIs, required for their activation against HIV-1,^[63] is unknown.^[61]

Administration of tenofovir disoproxil fumarate, a nucleotide reverse transcriptase inhibitor, with lopinavir/ritonavir in healthy volunteers did not result in clinically relevant alterations of pharmacokinetics of either drug (table III).^[59,60]

The oral bioavailability of both didanosine and lopinavir/ritonavir is significantly affected by concurrent food ingestion; the extent of their absorption is reduced (didanosine)^[64] or increased (lopinavir) [figure 1]^[14,15] by $\approx 50\%$ in the presence of food. Therefore, it is recommended that didanosine be administered 1 hour before or 2 hours after lopinavir/ritonavir has been taken with food.^[15]

4.2.2 Effect of Lopinavir/Ritonavir on Non-Antiretroviral Drugs

Both lopinavir and ritonavir inhibit CYP3A *in vitro*^[41] and *in vivo* and their combination is likely to increase plasma concentrations of other drugs metabolised through this pathway, thus increasing the risk of toxicity. The list of drugs potentially affected in this manner and the clinical recommendations for their concurrent use with lopinavir/ritonavir are presented in table IV.^[15,46,47]

In healthy volunteers, lopinavir/ritonavir 400/100mg twice daily significantly (statistical signifi-

Table IV. Drugs whose plasma concentration can be potentially significantly increased when coadministered with lopinavir/ritonavir and clinical recommendations for their dosage adjustment^[15,46,47,65]

Drug class (drug name)	Clinical recommendation
Antiarrhythmics (amiodarone, bepridil, lidocaine [systemic], quinidine)	Therapeutic drug plasma concentration monitoring
Immunosuppressants (cyclosporin, tacrolimus, rapamycin)	Therapeutic drug plasma concentration monitoring
Anti-infective agent (clarithromycin)	Dosage adjustment in patients with renal failure
Antimycobacterial agent (rifabutin ^a)	Use $\leq 25\%$ of usual dosage; ^b monitor closely for adverse events
Dihydropyridine calcium-channel blockers (e.g. felodipine, nifedipine)	Monitor closely for adverse events; adjust dosage accordingly
Erectile dysfunction agent (sildenafil)	Use with caution at 25mg every other day; monitor closely for adverse events
Lipid-lowering agent, HMG-CoA reductase inhibitor (atorvastatin ^a) ^[66]	Use lowest therapeutic dosage ^c or consider pravastatin; monitor closely for adverse events
Antifungal agents (ketoconazole, ^a itraconazole)	Dosages $>200\text{mg}$ once daily not recommended ^d

a Based on effects on the C_{max} and AUC in a study in 12 healthy volunteers receiving lopinavir/ritonavir 400/100mg twice daily.^[15,46,47]

b The usual dosage of rifabutin is 300mg once daily. Further dosage reduction may be necessary with long-term use.

c Start with $\leq 10\text{mg}$ of atorvastatin daily.

d Lopinavir/ritonavir induced a 3-fold increase in the AUC of ketoconazole as a 200mg single dose, although the change in the C_{max} was not significant.^[15,46,47]

AUC = area under the drug plasma concentration-time curve; **C_{max}** = peak plasma drug concentration.

cance established using 90% CI) reduced the C_{max} and AUC of methadone and ethinyl estradiol (suggesting the need for an alternative or backup method of contraception for HIV-1-positive women receiving the coformulation).^[15,46,47] In HIV-1 infected patients receiving lopinavir/ritonavir with stable doses of methadone, the C_{max} and AUC were similarly reduced;^[66] however, there was no requirement for methadone dosage adjustment and patients did not manifest opioid withdrawal symptoms.^[45,66] Finally, lopinavir/ritonavir may alter the plasma concentration of warfarin and therefore close monitoring of the international normalised ratio is recommended.^[15]

4.2.3 Effects of Non-Antiretroviral Drugs on Lopinavir/Ritonavir

Drugs that induce CYP3A isoenzymes may increase the clearance of lopinavir and lower its concentration in plasma, thus reducing its therapeutic efficacy. Hence, corticosteroids, particularly dexamethasone, which are potent inducers of CYP-mediated oxidative metabolism, should be used with caution in patients receiving lopinavir/ritonavir.^[15] Likewise, certain anticonvulsants (e.g. carbamazepine, phenytoin and barbiturates) may decrease lopinavir plasma concentrations and warrant appropriate dosage adjustment of the coformulation when administered concomitantly.^[15]

5. Therapeutic Efficacy

The therapeutic efficacy of lopinavir/ritonavir capsules and oral solution in combination with other antiretroviral agents has been evaluated in several clinical trials in patients with HIV infection.^[3,20,26,67,68] The majority of recent data are available only as abstracts or posters, although the 48-week results of three prospective, randomised, double-blind studies^[3,67,68] and a 6-month interim report from a 'national' EAP^[23] have been fully published.

Morbidity (e.g. incidence of opportunistic infections and malignancies) and mortality represent the primary clinical efficacy endpoints for antiretroviral therapy in patients infected with HIV-1. However, the clinical trials evaluating the lopinavir/ritonavir-based therapy in this patient population used two surrogate markers of disease progression to determine the efficacy of the coformulation: an immunological (i.e. CD4+ cell count) and a virological (i.e. plasma HIV-1 RNA level [viral load]) marker. Both

markers are highly predictive of disease progression to AIDS and death^[69-73] and are used to guide the decisions to initiate or change the treatment of HIV-1 infection and to assess its effectiveness. Trials in HIV-infected patients used surrogate markers. The effects of lopinavir/ritonavir on HIV-1- and AIDS-related morbidity and/or mortality are yet to be established.

Lopinavir/ritonavir has been evaluated in combination with other antiretroviral agents both in HIV-positive patients who had not previously received antiretroviral treatment (i.e. antiretroviral therapy-naïve patients)^[3,26,68] and in those who had received prior antiretroviral treatment (i.e. antiretroviral therapy-experienced patients).^[20,26,67,74-78] The lopinavir/ritonavir-based regimes have been evaluated both in comparative^[3,20,26,56,67,68] and noncomparative^[74-78] clinical trials and separately in adults^[3,20,56,67,68,74-78] and in children^[26] infected with HIV-1.

Results from clinical trials in this section are reported according to patients enrolled (intent-to-treat [ITT] analysis) and to evaluable patients who remained on study medication (on-treatment [OT] analysis) at the time of efficacy assessment. Virological responses (i.e. plasma HIV-1 RNA levels) are reported in both ITT and OT analyses, whereas immunological responses (i.e. CD4+ cell counts) correlate to OT analysis only.

All clinical trials evaluating the efficacy of lopinavir/ritonavir utilised two lower levels of quantitation (LLQs) for plasma HIV RNA levels: <400 copies/mL and <50 copies/mL; the latter LLQ represents a more reliable predictor of durable virological response to antiretroviral therapy.^[79]

5.1 In Adults

Thus far, four ongoing, prospective, randomised, multicentre clinical trials have investigated the efficacy of lopinavir/ritonavir in combination with either NRTIs^[3,68] or NRTIs plus an NNRTI^[20,67] in HIV-infected adults. Three trials^[3,67,68] were double-blind (table V) and one^[20] was nonblind. Two clinical trials included only antiretroviral therapy-naïve patients (table V).^[3,68] The other two trials included only NNRTI-naïve patients with a history of treatment with a single (i.e. single PI-experienced patients) [table V]^[67] or multiple (i.e. multiple PI-experienced patients) PI's.^[20] The phase II trials compared the efficacy of various dose combinations of lopinavir coformulated with ritonavir. The only

Table V. Summary of randomised, double-blind, multicentre clinical trials of lopinavir/ritonavir (LPV/r) in adult patients (pts) with HIV infection. All treatment regimens were administered twice daily unless stated otherwise

Reference	No. of pts (duration of treatment [w])	Treatment regimen (mg)	Plasma viral load (log ₁₀ copies/mL)		CD4+ count (cells/ μ L)	Pts with plasma viral load below LLQ (%)		
			baseline	change at week 2		baseline	change at study end	<400 copies/mL (ITT/OT)
Dose-comparison trial in antiretroviral therapy-naïve patients								
Murphy et al. ^[3]	16 (48) [group I ^a]	LPV/r 200/100 +3TC +d4T ^b	4.88	↓1.73 ^c	471	↑205 ^d	100/100	100**/100
	16 (48) [group I ^a]	LPV/r 400/100 +3TC +d4T ^b	4.96	↓1.73 ^c	330	↑276 ^d	81/93	50/57
	35 (48) [group II]	LPV/r 400/100 +3TC +d4T ^b	4.78	↓1.68 ^e	343	↑226 ^d	91/100*	86/94
	33 (48) [group II]	LPV/r 400/200 +3TC +d4T ^b	4.97	↓1.68 ^e	275	↑197 ^d	80/80	73/73
Comparison vs nelfinavir (NFV) in antiretroviral therapy-naïve patients								
Walmsley et al. ^[68]	326 (48)	LPV/r 400/100 +3TC +d4T ^b	4.89		260	↑207	75***/93***	67***/83***
Johnson et al. ^[63] /g	326 (60)					↑247	74***/NR	64**/NR
Ruane et al. ^[64]	327 (48)	NFV 750 tid +3TC +d4T ^b	4.92		258	↑195	63/82	52/68
	327 (60)					↑224	61/NR	52/NR
Dose-comparison trial in single PI-experienced, NNRTI-naïve patients								
Benson et al. ^[67]	36 (48)	LPV/r 400/100 ^h +NVP ⁱ +2 NRTIs ^j	4.1	↓1.21	371	↑140	67/79	56/64
Hicks et al. ^[65] /k	36 (144)					↑177	53/83	44/73
	34 (48)	LPV/r 400/200 ^h +NVP ⁱ +2 NRTIs ^j	4.0	↓1.07	372	↑108	74/93	68/89
	34 (144)					↑254	56/86	53/78

a d4T and 3TC added from week 3.

b d4T and 3TC were administered nonblind.

c Combined data from group I.

d Data estimated from a graph.

e Combined data from group II.

f Poster.

g OT analysis data.

h Patients received separate capsules of LPV and r until coformulated capsules became available. LPV was given nonblind while r was given double-blind.

i From day 15 patients received NVP od for 2 weeks and bid thereafter.

j On day 15 NRTI regimen was changed to include ≥ 1 novel NRTI. Actual drugs not reported.

k Abstract and poster.

d4T = stavudine 40; ITT = intent-to-treat analysis; LLQ = lower limit of quantitation; NNRTI = non-nucleoside reverse transcriptase inhibitor; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine 200; od = once daily; OT = on-treatment analysis; pts = patients; tid = three times daily; viral load = HIV-1 RNA level; 3TC = lamivudine 150; ↓ indicates decrease; ↑ indicates increase; * p = 0.01; ** p = 0.002; *** p < 0.001 vs comparator regimen.

phase III trial conducted thus far compared the efficacy of lopinavir/ritonavir- versus nelfinavir-containing antiretroviral regimen in HIV-infected adult patients (table V).^[68]

The efficacy of lopinavir/ritonavir coformulation was also assessed in two prospective, nonblind, noncomparative studies (the EAP and the ATU programme) involving >11 000 HIV-1-infected patients who had failed to respond to and/or were intolerant to various combinations of available antiretroviral agents. In these patient populations lopi-

navir/ritonavir-based regimens were evaluated as salvage therapy options.^[74-78]

5.1.1 Antiretroviral Therapy-Naïve Patients

Dose-Comparison Trial

Antiretroviral therapy-naïve HIV-infected adults (age ≥ 18 years) were enrolled sequentially into two groups (group I excluded patients coinfecting with hepatitis B and/or C virus [HBV/HCV]). Patients were then randomised to receive one of two dosage regimens of lopinavir/ritonavir (group I: 200/100mg or 400/100mg twice daily; group II: 400/100mg or

400/200mg twice daily) in combination with lamivudine and stavudine (table V).^[3] Inclusion criteria were based predominantly on plasma HIV-1 RNA levels with no CD4+ cell count restriction; hence patients in this phase II study presented with a relatively high mean plasma viral load and a wide range of immunological responsiveness at baseline.

In the initial 48-week study, the lopinavir/ritonavir combinations reduced plasma HIV-1 RNA and increased mean CD4+ cell counts when combined with two commonly used NRTIs in antiretroviral therapy-naïve patients (table V).^[3] Overall, the mean reduction in plasma HIV-1 RNA from baseline was 2.23 log₁₀ copies/mL, and 85% and 92% of patients (ITT and OT analyses) had <400 copies/mL at the study end.^[3] Median time required for plasma viral load to decrease below 400 and 50 copies/mL was 6–8 and 10–12 weeks, respectively. Patients with baseline viral load >5 log₁₀ copies/mL generally required more time to achieve a viral load <400 copies/mL than patients with baseline values of <5 log₁₀ copies/mL (12 vs 4 weeks).^[3] However, all lopinavir/ritonavir-based regimens showed sustained viral suppression at and beyond 20 weeks of treatment regardless of baseline viral load.^[3] Patients in all treatment groups also showed a substantial increase (i.e. 44–84%) in the mean CD4+ cell count at week 48 (table V).^[3]

In the extension of this study, after the 48-week trial the dosage of lopinavir/ritonavir was changed to 400/100mg twice daily in all patients and the study was continued in a nonblind fashion. The follow-up results to week 204 showed continued suppression of viral load below LLQ in a substantial proportion of patients by both ITT and OT analyses (figure 2).^[80–82]

The effects of the lopinavir/ritonavir-based treatment on viral load and CD4+ cell count were not influenced by patient baseline virological or immunological status. For example, after 144 weeks of treatment with the lopinavir/ritonavir-based regimen, the proportion of patients with plasma HIV-1 RNA levels of <50 copies/mL was similar between patients with higher (≥ 5 log₁₀ copies/mL) and lower (<5 log₁₀ copies/mL) baseline viral loads (92% vs 100% and 80% vs 73%; OT and ITT analyses, respectively).^[82] Likewise, similar proportions of patients with higher (≥ 200 cells/ μ L) and lower (<200 cells/ μ L) baseline CD4+ cell counts had their viral load reduced below 50 copies/mL (98% vs 94% and 72% vs 83%; OT and ITT analyses, re-

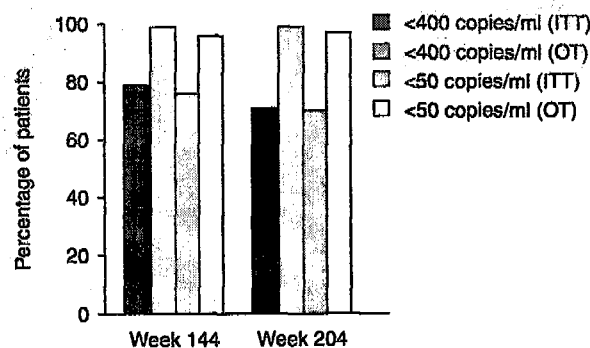


Fig. 2. The effect of lopinavir/ritonavir on plasma HIV-1 RNA levels in HIV-1 infected adults. Results from the extension phase (up to week 204) of a randomised, double-blind, dose-comparison trial in 100 antiretroviral therapy-naïve patients.^[3] In the nonblind extension phase, after the initial 48-week trial all patients received lopinavir/ritonavir 400/100mg twice daily, in addition to lamivudine 150mg and stavudine 40mg twice daily.^[17,80–82] On-treatment (OT) and intent-to-treat (ITT) analyses are presented for limits of quantitation of <400 and <50 HIV-1 RNA copies/mL.

spectively).^[82] At week 204, the Kaplan-Meier estimate of the proportion of patients still maintaining virological response was 84.1%.^[17]

The immunological status of patients who remained on treatment with lopinavir/ritonavir-based antiretroviral regimen continued to improve steadily and at week 204 the mean increase from baseline in their CD4+ cell count was 440 cells/ μ L.^[17] Only 8 of 79 patients remaining on-treatment at weeks 144–156 had an increase from baseline in CD4+ cell count of <100 cells/ μ L. However, the final values in all eight patients were >500 cells/ μ L.^[81] The rate and the amount of increase in CD4+ cell count appeared to be consistent regardless of patient baseline immune status.^[17,80,81] Even patients with the most advanced disease (baseline CD4+ cell count <50 cells/ μ L; n = 17) achieved a mean increase of 423 cells/ μ L in CD4+ count at week 204.^[17]

In Comparison with Nelfinavir

A large phase III study compared the efficacy of lopinavir/ritonavir with the PI nelfinavir in combination with two NRTIs, lamivudine and stavudine, in 653 antiretroviral therapy-naïve adult (age ≥ 12 years) patients with HIV infection (table V).^[68,83,84] Lopinavir/ritonavir demonstrated significantly greater suppression of plasma HIV-1 RNA levels than nelfinavir, starting from week 20 (LLQ <400 copies/mL) and week 32 (LLQ <50 copies/mL) and persisting through weeks 48 and 60 (table V).^[68,84] Patients treated with lopinavir/ritonavir showed only a slightly higher increase from baseline

Table VI. Comparative efficacy of lopinavir/ritonavir versus nelfinavir in relation to baseline hepatitis status. Week 60 results from a randomised, double-blind, multicentre trial in antiretroviral therapy-naïve HIV-1-positive adults.^[87] On-treatment analyses are presented

Baseline hepatitis status ^a	No. of patients (% of total)	Mean age (y)	M/F (%)	Plasma viral load (log ₁₀ copies/mL)	CD4+ count (cells/μL)		Patients with plasma viral load below LLQ (%)	
					baseline	mean increase	<400 copies/mL	<50 copies/mL
Lopinavir/ritonavir 400/100mg bid ^b								
Positive	57 (17.5)	41	82/18	4.8	283	246 ^c	91	76
Negative	269 (82.5)	38	79/21	4.9	255	247 ^c	96	84
Nelfinavir 750mg tid ^b								
Positive	68 (21)	37	78/22	5.0	244	233 ^c	79	70
Negative	259 (79)	37	81/18	4.9	261 ^d	219 ^c	88	75

a On enrolment, all patients were screened for hepatitis B surface antigen and anti-hepatitis C antibody. Patients were then classified as hepatitis positive if either test was positive.

b All patients also received lamivudine 150mg and stavudine 40mg bld in a nonblind fashion.

c Data estimated from a graph.

d One patient did not have a baseline CD4+ cell count measurement.

bld = twice daily; F = female; LLQ = lower limit of quantitation; M = male; tid = three times daily; viral load = HIV-1 RNA level.

in the mean CD4+ cell count than patients treated with nelfinavir (table V).^[3] However, in patients with very low CD4+ cell counts at baseline (<50 cells/μL), lopinavir/ritonavir induced a significantly greater increase in the mean CD4+ cell count compared with nelfinavir after 60 weeks of treatment (266 vs 198 cells/μL; $p < 0.05$).^[84]

Treatment with the lopinavir/ritonavir-based triple regimen was equally as effective in women as in men with HIV-1 infection, as determined by the percentage of patients with <50 HIV-1 RNA copies/mL (83% vs 82% and 61% vs 65%; OT and ITT analyses, for respective sexes) and by the mean increase from baseline in CD4+ cell count (257 vs 244 cells/μL).^[86]

Patients receiving lopinavir/ritonavir-based triple therapy had a significantly greater probability of maintaining virological response at 48 and 60 weeks than recipients of nelfinavir-based regimen (84% vs 66% and 81% vs 65%, both $p < 0.001$ between treatment regimens).^[68,84]

A subgroup of 125 patients (lopinavir/ritonavir = 57, nelfinavir = 68) in this study were coinfectd with HBV/HCV.^[87] Baseline immunological, virological and demographic characteristics of HBV/HCV positive and negative patients were similar between the treatment groups (table VI).^[87]

After 60 weeks, on-treatment antiviral responses (at LLQ <400 and <50 HIV-1 RNA copies/mL) and immunological response rates (measured as increase in CD4+ cell count) of patients within lopinavir/ritonavir- and nelfinavir-treatment groups were sim-

ilar in relation to patients' baseline hepatitis status (table VI).^[87]

5.1.2 Antiretroviral Therapy-Experienced Patients

Single PI-Experienced, NNRTI-Naïve Patients

A dose-comparison phase II trial investigated the efficacy of lopinavir 400mg coformulated with ritonavir 100 or 200mg twice daily for 144 weeks in 70 adult (age ≥18 years) HIV-1-infected patients who were experiencing virological failure (defined as plasma HIV-1 RNA level of 3–5 log₁₀ copies/mL) with treatment regimen comprising a single PI, alone or combined with one or more NRTI (table V).^[67,85] The existing PI regimen of all patients was replaced with one of the two lopinavir/ritonavir dose combinations on day 1 of the study. All patients also received nevirapine (200mg once daily for 2 weeks from day 15, followed by 200mg twice daily thereafter) and had their baseline NRTI regimen changed on day 15 to include at least one NRTI they had not received previously. Ritonavir was administered in a double-blind fashion, whereas lopinavir, nevirapine and NRTIs were administered nonblind.^[67]

The lopinavir/ritonavir-based regimen induced rapid viral suppression with 80% of patients experiencing ≥1 log₁₀ copies/mL reduction from baseline in plasma HIV-1 RNA levels or achieving a viral load of <400 copies/mL, within the first 2 weeks of treatment.^[67] These results were maintained at 48 weeks and for the duration of the study in patients who continued lopinavir/ritonavir-based salvage therapy (table V).^[85]

The susceptibility towards lopinavir, the principal component of the drug with antiretroviral activity, was variable in HIV-1 isolated from patients enrolled in this study. The baseline HIV-1 isolates were 0.7–26 (mean 2.8) times less susceptible to lopinavir than the wild-type HIV-1 (as determined by fold increase in IC₅₀).^[67,85] The initial viral load decline was independent of both the baseline HIV-1 IC₅₀ for lopinavir and the prior PI experience of the study participants.^[67,85]

Throughout the study and up to week 144, no statistically significant difference in the antiviral activity was recorded between the two lopinavir/ritonavir dose combinations.^[67,85] At week 144, more than half of all patients enrolled still had plasma HIV-1 RNA levels suppressed below 400 copies/mL (table V) and in almost half of them (49% overall) it was below 50 copies/mL.^[85]

The lopinavir/ritonavir-based salvage therapy induced a rapid improvement in CD4+ lymphocyte count and statistically significant increase from baseline was observed in both treatment groups at and after week 8 ($p < 0.001$).^[67] The mean overall increase from baseline in CD4+ cell count at week 144 was 211 cells/ μ L with no statistically significant difference between treatment groups observed at any timepoint (table V).^[85]

Multiple PI-Experienced, NNRTI-Naïve Patients

A smaller randomised, nonblind trial in multiple PI-experienced (mean prior PIs = 3) but NNRTI-naïve HIV-infected adult patients ($n = 57$; age >18 years) compared the efficacy of two lopinavir/ritonavir dose combinations (i.e. 400/100mg vs 533/133mg twice daily) in an antiretroviral regimen containing efavirenz 600mg once daily and NRTIs of the investigators' choice over the 24-week period (results presented only in an abstract and a poster).^[56]

Upon enrolment all patients were randomised into two study arms (A and B) and had their current PI replaced with lopinavir/ritonavir 400/100mg which they received twice daily in combination with efavirenz and NRTIs (actual drugs not specified) for the first 13 days of the study. Preliminary pharmacokinetic analyses for lopinavir and efavirenz were performed in all patients at day 14. Following that, patients in arm A ($n = 29$) continued treatment with the same regimen until week 24, while the patients in study arm B ($n = 28$) had their lopinavir/ritonavir

dosage increased to 533/133mg twice daily for the duration of the trial.

After 24 weeks, the study became noncomparative as all patients in study arm A converted to the 533/133mg twice-daily dosage of lopinavir/ritonavir. The rationale for the dose increase was provided by pharmacokinetic analyses performed at week 5 showing that efavirenz reduced lopinavir plasma concentrations achieved with lopinavir/ritonavir 400/100mg twice daily compared with historical data in HIV-infected adults receiving lopinavir/ritonavir without efavirenz (section 4.2.1 and table III).

Treatment with the lopinavir/ritonavir 533/133mg twice-daily regimen resulted in a similar degree of plasma viral load suppression (92% vs 80% of patients had plasma HIV-1 RNA <400 copies/mL; OT analysis)^[88] and a similar increase in the CD4+ cell count (41 vs 48 cells/ μ L)^[56] from baseline, to that with the 400/100mg regimen at week 24. In the extension of the study, treatment with the lopinavir/ritonavir 533/133mg twice-daily regimen maintained this level of viral load suppression up to week 72 (67% and 61% of the ITT population, and 88% and 81% of the OT population had HIV-1 RNA <400 and <50 copies/mL, respectively). The CD4+ cell count continued to improve and at week 72 the mean increase from baseline among patients on treatment was 126 cells/ μ L.^[20]

Baseline *in vitro* phenotypic and genotypic susceptibility to lopinavir of viral isolates had an important influence on virological response throughout the course of the study (section 2.3.2).^[19-21]

Multiple PI-Experienced, NNRTI-Experienced Patients with Virological Failure

The efficacy of lopinavir/ritonavir coformulation has also been evaluated through the prospective, nonblind, noncomparative EAP.^[74-77] This study recruited >11 000 HIV-1-infected adult patients from 35 countries with significant prior exposure to both PIs and NNRTIs. These patients had failed to respond to and/or were intolerant to combinations of other available antiretroviral agents and in many, disease stage was advanced at study enrolment (table VII). The bulk of the available data from the EAP are from four representative countries (i.e. Italy,^[74] Germany,^[75] Canada,^[76] and Spain^[77]) and are derived from posters and abstracts. Baseline demographic and disease characteristics of patients in each 'national' EAP were generally similar (table VII). The mean duration of follow-up ranged be-

Table VII. Overview of baseline demographic and disease characteristics of participants in the ATU programme and in the Expanded Access Program (EAP) in four representative countries

Country of data origin (no. of evaluable pts)	Mean age (y)	M/F (%) ^a	Clinical category according to CDC classification for HIV infection ^[88] (% of pts) ^a			Karnofsky score (mean)	Plasma HIV-1 RNA level		CD4+ cell count	
			A ^b	B ^c	C ^d		mean (log ₁₀ copies/mL)	≥4 log ₁₀ copies/mL (% of pts)	mean (cells/μL)	<200 cells/μL (% of pts)
Germany (684) ^[76]	43.0	87/12	7.9	31.7	57.2	88.3	4.41	67.5	215	55.6
Italy (1265) ^[74]	39.9	68/24	22.0	24.7	39.1	91.6	4.66	70.8	224	47.7
Spain (1772) ^[77]	39.2	74/23	22.6	23.6	44.3	96.2	4.37	62.1	277	42.9
Canada (1256) ^[76]	42.6	91/8	17.6	35.5	42.0	88.4	4.34	62.3	210	57.4
ATU programme (3447) ^[78]	42.0	80/20	16.8	31.9	51.3		4.66	84.0	202	62.0

a Unspecified data not presented; percentages from the EAP do not add up to 100.

b Asymptomatic or acute (primary) HIV or persistent generalised lymphadenopathy.

c Symptomatic, neither A nor C conditions.

d AIDS-indicator conditions.

ATU = Autorisation Temporaire d'Utilisation; CDC = Centers for Disease Control; F = female; M = male; pts = patients.

tween 4.5^[75] and 8.6^[76] months. In France the EAP was rapidly switched to an ATU programme in which potentially-lifesaving medications are made available to patients prior to their approval.^[25,78] Genotype analysis of viral isolates was performed at baseline in the ATU programme but not the EAP. In both studies, patients received lopinavir/ritonavir 400/100mg twice daily either in tablet or liquid form. The dosage was increased to 533/133mg if concomitant treatment included nevirapine or efavirenz.

In the EAP, >50% of patients achieved a viral load of ≤500 copies/mL (some data estimated from graphs).^[74-77] When the virological response criteria were expanded to also include patients with ≥1 log₁₀ copies/mL reduction from baseline, an

overall response was observed in ≈75% of patients (some data estimated from graphs).^[74-77] Similarly, in the ATU programme, ≈72% of patients achieved virological response (defined as plasma HIV-1 RNA level <400 copies/mL or ≥1 log₁₀ copies/mL decrease from baseline) after 6-month treatment with lopinavir/ritonavir-based regimens.^[25] Both studies showed a strong correlation between baseline CD4+ cell count, lopinavir mutation score and prior PI use and the virological response to the lopinavir/ritonavir-based treatment of HIV-1 infection ($p < 0.01$).^[25]

An association between the lopinavir mutation score as well as the individual PI mutations (including lopinavir) present at baseline and the virological response to lopinavir/ritonavir was observed in the

Table VIII. Efficacy of lopinavir/ritonavir in antiretroviral therapy-naïve and -experienced children with HIV-1 infection. All patients (pts) received lopinavir/ritonavir 300/75 mg/m² twice daily in oral solution. Week 72 results from a nonblind, phase I/II study.^[26] Intent-to-treat analyses are presented

Antiretroviral therapy-related pts status ^a	No. of pts	Mean age (y)	M/F (%)	Plasma viral load (log ₁₀ copies/mL)		CD4+ count (cells/μL)		Pts with plasma viral load below LLQ (%)	
				baseline		baseline	mean increase	<400 copies/mL	<50 copies/mL
Naïve ^b	44	4.8	41/59	4.9		920*	387	89	71
Experienced ^c	56	5.7	45/55	4.5		773	435	68	55

a Pts were defined as naïve or experienced if they had received ≤3 months or >3 months of prior antiretroviral therapy and ≤1 week or >1 week of treatment with lamivudine, respectively.

b Pts received additional treatment with stavudine and lamivudine.

c Pts received additional treatment with nevirapine and one or two NRTIs of the investigator's choice.^[26] Dosage of nevirapine was 7 mg/kg bid for pts aged 6m to 8y or 4 mg/kg bid for older pts.^[15]

F = female; LLQ = lower limit of quantitation; M = male; NRTI = nucleoside reverse transcriptase inhibitor; viral load = HIV-1 RNA level; * $p < 0.05$ between patient groups.

Spanish EAP^[23] and the ATU^[24,25,90] (see section 2.3.3 for details).

5.2 In Children

The clinical efficacy of lopinavir/ritonavir liquid formulation has been evaluated in a nonblind, phase I/II study in antiretroviral therapy-naïve (≤ 3 months of prior antiretroviral therapy and ≤ 1 week of treatment with lamivudine; $n = 44$) and -experienced ($n = 56$) patients (children aged between 3 months and 12 years) infected with HIV-1 (presented as a poster^[26]). All patients were initially randomised to receive lopinavir/ritonavir 230/57.5 mg/m² ($n = 49$) or 300/75 mg/m² ($n = 51$) in oral solution once every 12 hours. These dosages were chosen to mimic the exposure to lopinavir achieved in adults after administration of lopinavir/ritonavir 400/100mg twice daily. After the week 3 pharmacokinetic, tolerability and efficacy analyses, dosage of the study drug was changed to 300/75 mg/m² twice daily for all study participants. In addition to lopinavir/ritonavir, all patients also received lamivudine and stavudine (antiretroviral therapy-naïve patients), or nevirapine and 1–2 NRTI agents of the investigator's choice (antiretroviral therapy-experienced patients) [nevirapine regimen was 7 or 4 mg/kg twice daily, for patients aged 6 months to 8 years or for older children, respectively;^[15] dosages of NRTIs, including lamivudine and stavudine, were not specified].^[26]

Demographic characteristics and the virological status at baseline of patients in both groups in this study were similar (table VIII). However, patients naïve to antiretroviral drug treatment had higher CD4+ cell counts at baseline than the experienced patients ($p < 0.05$) [table VIII]. Most patients in this study had acquired HIV-1 infection in the perinatal period (98% and 95% of antiretroviral therapy-naïve and -experienced patients, respectively).

After 72 weeks, lopinavir/ritonavir-based treatment regimens adequately suppressed plasma HIV-1 RNA levels in most patients, although overall responses tended to be lower in antiretroviral therapy-experienced patients (table VIII). A larger proportion of PI-naïve, NRTI-experienced patients ($n = 32$) had viral load suppressed below 400 copies/mL than patients previously treated with both PI and NRTI agents ($n = 24$) [81% vs 50%; p -value not reported]. The immune status of patients in each group continually improved throughout the study

and at week 72 the mean increase from baseline in CD4+ cell count was 11.2%, 9.2% and 7.7% in antiretroviral therapy-naïve, PI-/NRTI-experienced, and PI-naïve/NRTI-experienced patients, respectively.^[26]

Antiviral activity of lopinavir/ritonavir in PI-experienced patients was influenced by baseline phenotype resistance of HIV-1 isolates (section 2.3.4).^[26]

6. Tolerability

It is difficult to precisely attribute causality of adverse events to treatment with the lopinavir/ritonavir coformulation as associations are confounded by patients' concomitant therapies and the severity of their illness.

The tolerability of the lopinavir/ritonavir coformulation in combination with other antiretroviral agents has been evaluated in both antiretroviral therapy-naïve^[26,80,84,91] and -experienced^[20,26,74-77,85,91] patients infected with HIV-1, in comparative^[20,26,80,84,85,91] and noncomparative^[74-77] clinical trials, and separately in adults^[20,74-77,80,84,85,91] and children.^[26] Overall in these trials and patient populations lopinavir/ritonavir appeared to be well tolerated, with low rates of drug-related discontinuation of therapy (table IX).^[84,91]

6.1 In Adults

6.1.1 Comparative Trials

Tolerability of lopinavir/ritonavir has been evaluated in 553 HIV-1-infected adults from four randomised, comparative, phase II/III clinical trials (see section 5.1 and table V for study details; see table IX for summary of adverse events and laboratory abnormalities).^[20,80,84,85,91]

The tolerability profile of lopinavir/ritonavir 400/100mg twice daily in the phase III trial was generally similar to that of nelfinavir 750mg three times daily (table IX).^[91] The most frequently reported adverse event of at least moderate severity was diarrhoea in both phase II^[80,85,91] and phase III^[91] clinical trials and in both antiretroviral therapy-naïve^[80,91] and -experienced^[85,91] patients. Other less common events included other gastrointestinal (GI) disturbances, asthenia, headache and skin rash.^[91] Circumoral paraesthesia has not been reported with lopinavir/ritonavir administration. In some instances the incidence of specific adverse events in dose-

Table IX. Incidence of adverse events of at least moderate severity (causality not established) and of grade 3/4^a laboratory abnormalities in four randomised, comparative^b phase II/III lopinavir/ritonavir (LPV/r) clinical trials in adult patients (pts) with HIV-1 infection^[20,80,84,85,91]

Results (% of pts)	Phase III ARV-naïve pts (60w) ^[91]		Phase II ARV-naïve pts (204w) ^[17]	Phase II single PI-exp pts (144w) ^[85]	Phase II multiple PI-exp pts (48w; ^[91] 72w ^[20])
	LPV/r+d4T+3TC (n = 326)	NFV+d4T+3TC (n = 327)	LPV/r+d4T+3TC (n = 100)	LPV/r+NVP+2 NNRTIs (n = 70)	LPV/r+EFV+NNRTIs (n = 57)
Adverse events					
Diarrhoea	17	18	28	31	12
Nausea	7	5	16	3	4
Asthenia	4	3	8	6	11
Abdominal pain	4	3	10	0 ^c	5
Vomiting	3	2	6	1 ^c	2
Headache	3	2	8	1 ^c	4
Rash	1 ^d	2 ^d	4 ^e	3 ^c	2
Laboratory abnormalities^f					
	(60w)	(60w)	(204w)	(144w)	(72w)
Total cholesterol (>7.77 mmol/L)	11	6	22	31	40
Triglycerides (>8.25 mmol/L)	11 [*]	2	22	22	40
AST/ALT (>5 x ULN)	6	5	11	11	4
Amylase (>2 x ULN)	4	2	5 ^g	6	11
Glucose (>13.75 mmol/L)	2	2	2 ^g	3	5
LPV/r-related therapy discontinuations	4	4 ^h	7 ⁱ	6 ^c	5

a Severity grades based on the Division of AIDS Grading Severity of Adult Adverse Events criteria.

b Phase II trials compared different dosages of lopinavir/ritonavir administered twice daily. The results from a trial in single PI-experienced pts are presented for the 400/100mg cohort only,^[85] with the exception of the combined results for week 96 data. In the extension phases, after 48 and 24 weeks, of the respective trials in the ARV-naïve^[80] and the multiple PI-experienced^[20,91] pts, all participants received lopinavir/ritonavir 400/100mg and 533/133mg, respectively, twice daily.

c Combined results for the LPV/r 400/100mg and 400/200mg cohorts at week 96.^[91]

d Week 48 data.^[15]

e Week 144 data.^[91]

f Determination of laboratory values were performed without regard to fasting.

g Week 72 data.^[16]

h Data from Ruane et al.^[84]

i Including one death of unknown cause 10 days after thoracic spinal surgery with perioperative myocardial infarction.

ARV = antiretroviral therapy; d4T = stavudine; EFV = efavirenz; exp = experienced; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; ULN = upper limit of normal; 3TC = lamivudine; * p < 0.001 between comparator groups.

comparison phase II trials was higher than in the phase III trial.^[80,85,91] This may be a consequence of a longer follow-up in the phase II than the phase III trial (204 or 144 vs 60 weeks) as well as of the addition of specific NNRTIs (nevirapine or efavirenz) to the treatment regimens in particular phase II trials (see table IX for details). The tolerability results from these phase II trials could have been also confounded by the use of different dosages of lopinavir/ritonavir in the initial, dose-comparison (i.e. 200/100mg, 400/100mg, 400/200mg or 533/133mg twice daily; see section 5.1 and table V

for study details) and the trial extension, noncomparative phases (i.e. 400/100mg or 533/133mg twice daily) and by the smaller patient populations evaluated in phase II trials than in the phase III trial (table IX).

Over 60 weeks of treatment in the phase III study, 7% of patients (antiretroviral therapy-naïve) in the lopinavir/ritonavir and nelfinavir groups had adverse events consistent with changes in body fat composition. In the lopinavir/ritonavir group these changes included lipodystrophy, obesity and abdomen enlargement (2% each), and Cushingoid ap-

pearance, multiple lipomas and gynaecomastia ($\leq 1\%$ each). None of these changes were associated with grade 3/4 lipid elevations.^[91]

In three dose-comparison, phase II trials, changes in body fat composition occurred in 12% (week 144), 20% (week 96) and 7% (week 48) of antiretroviral therapy-naïve, single PI- and multiple PI-experienced patients, respectively.^[91]

In all comparative, phase II/III clinical trials, lopinavir/ritonavir administration was associated with marked laboratory abnormalities (table IX), with grade 3/4 lipid (total cholesterol and triglycerides) elevations being the most common.^[20,80,85,91] Both abnormalities tended to occur early in the course of treatment, remained stationary over time and were more common in patients with prior PI experience or higher baseline lipid levels. However, they were a rare cause of study drug discontinuations and responded well to treatment with lipid-lowering agents (but see section 4.1).^[91]

In the phase III trial, laboratory abnormalities occurred with similar frequency in both treatment groups (table IX), with the exception of grade 3/4 elevations in triglycerides levels, which occurred more frequently in the lopinavir/ritonavir than in the nelfinavir group (11% vs 2%; $p < 0.001$). Importantly, though, grade 3/4 triglyceride elevations were not associated with development of pancreatitis or discontinuation of treatment in patients receiving either drug.^[91]

It should be noted that in the phase II/III trials the measurements were taken without regard to fasting.^[84,91]

The tolerability profile of lopinavir/ritonavir was similar in HBV/HCV positive and negative patients with HIV-1 infection (see section 5.1.1 and table VI for study details).^[87] The incidence of grade 3/4 laboratory abnormalities through week 60 were similar in both patient groups, although ALT elevation (>5 -fold upper limit of normal [ULN]) was significantly more frequent in HBV/HCV positive than in hepatitis negative patients (12% vs 3%; $p < 0.05$).^[87] No patients discontinued treatment with lopinavir/ritonavir because of an abnormal liver function test or a diagnosis of clinical hepatitis.^[87]

6.1.2 Noncomparative Trials

In the EAP (see section 5.1.2 and table VII) only serious adverse events of possible, probable or unknown relationship to lopinavir/ritonavir were reported as per protocol. Although a number of differ-

ent events (including myocardial infarction,^[76] pancreatitis,^[75-77] lactic acidosis^[74] and hepatic failure^[77]) were reported in each 'national' EAP, none occurred in $\geq 1\%$ of study participants during the mean follow-up period of ≈ 4.5 –8.5 months.^[74-77]

The overall incidence of adverse events in the French ATU programme (see section 5.1.2 and table VII) was not higher than that generally reported with other antiretroviral regimens in experienced patients, with 836 (22%) events occurring in 356 of 3819 enrolled (9%) patients. The majority of adverse events were related to the GI system and the body as a whole (7.1% and 5.5%, respectively), with diarrhoea, nausea and vomiting, and abdominal pain, asthenia and fever being the most common events in the respective categories. Drug-related diabetes mellitus and pancreatitis both occurred in $\approx 0.1\%$ of cases. Hyperlipidaemia and hypercholesterolaemia were reported in $< 1\%$ of patients. Discontinuations of treatment because of adverse events of possible, probable or unknown relationship to lopinavir/ritonavir were also infrequent (2%) and were primarily related to GI adverse events. There were no study drug-related deaths during the course of the programme.^[92]

In addition, a recent case report described two patients with AIDS who developed potentially fatal bradyarrhythmia shortly after commencement of lopinavir/ritonavir 400/100mg twice daily as part of antiretroviral therapy.^[93]

6.2 In Children

The liquid formulation of lopinavir/ritonavir 300/75 mg/m² administered twice daily was very well tolerated by antiretroviral therapy-naïve ($n = 44$) and -experienced ($n = 56$) HIV-1-infected children, with only one lopinavir/ritonavir-related discontinuation of the treatment up to week 72 (pancreatitis in a child with elevated baseline amylase levels).^[26]

The incidence of adverse events of at least moderate severity and of probable or possible relationship to lopinavir/ritonavir was low; the most commonly reported adverse event occurring in 2% of patients was skin rash; allergic reactions, fever, viral infections, constipation, hepatomegaly, pancreatitis, vomiting, dry skin and taste perversion all occurred in 1% of patients.^[26] Development of lipodystrophy was not reported in this study.

Biochemical abnormalities of grade 3/4 severity were also infrequent occurring in 6% (amylase $>2.5 \times \text{ULN}$), 5% (AST/ALT $>10 \times \text{ULN}$) and $\leq 3\%$ (total bilirubin $>2.9 \times \text{ULN}$, total cholesterol $>7.7 \text{ mmol/L}$, triglycerides $>8.25 \text{ mmol/L}$ and pancreatic amylase $>2 \times \text{ULN}$) of patients.^[26]

7. Pharmacoeconomic Analyses

Thus far, two pharmacoeconomic models have been used to estimate the 60-week,^[94] 5-year^[95,96] and lifetime^[95,96] cost consequences of initiating antiretroviral therapy with lopinavir/ritonavir versus nelfinavir as the PI component in the triple regimen (in combination with lamivudine and stavudine). Both models utilised the results from a phase III study (section 5.1.1) in 625 antiretroviral therapy-naïve HIV-infected patients and are reported as abstracts.^[94-96]

The benefit of 22.1% higher 60-month response rate (at $<400 \text{ HIV-1 RNA copies/mL}$) with lopinavir/ritonavir compared with nelfinavir conveyed a potential net cost savings (calculated in 2002 \$US) of \$US1454.14 per patient per 60 months of treatment in a decision-tree cost-analysis model.^[94] The acquisition costs for both drugs were assumed equal, the cost of therapy included antiretroviral drugs, clinical visits and, for patients who failed to respond to treatment, drug resistance testing, additional monitoring and treatment of AIDS-related events. When the regimen for patients who failed to respond to therapy was changed to two PIs plus two NRTIs, a PI plus an NNRTI plus two NRTIs, or a PI plus two NRTIs, the estimated cost savings per patient were \$US2704.38, \$US1928.46, and \$US838.35, respectively, over 60 months.^[94]

In a cost-utility analysis, potential 5-year cost savings per patient were estimated to be \$US4011 for lopinavir/ritonavir compared with nelfinavir,^[96] assuming an acquisition cost of \$US18 per day for either drug and an estimated 5-year treatment response rate of 26% and 23% for each regimen, respectively.^[95] The estimated incremental cost effectiveness ratio was \$US3423 per quality-adjusted life-year (QALY) for lopinavir/ritonavir versus nelfinavir, which is comparable to values calculated for generic antihypertensive medications.^[96] As the second model also predicted median survival of 13.3 and 12.8 years, respectively, for patients initiating therapy with lopinavir/ritonavir and nelfinavir, the lifetime benefit of the former treatment was estimat-

ed at \$US18 899 per QALY compared with the latter treatment.^[95] In the second model currency years were not stated, nor were discount rates mentioned.

8. Dosage and Administration

Coformulated lopinavir/ritonavir is available for oral administration in capsule (133.3mg lopinavir and 33.3mg ritonavir) and liquid (80/20 mg/mL) formulations.^[15] The recommended dosage for adults, in the US, for the treatment of HIV-1 infection is 400/100mg (three capsules or 5mL oral solution) twice daily.^[15] In children aged 6 months to 12 years, the recommended dosage of the oral solution is 12/3 mg/kg for those 7 to $<15 \text{ kg}$ of bodyweight and 10/2.5 mg/kg for those 15–40kg (approximately equivalent to 230/57.5 mg/m²) administered twice daily.^[15] In the US, the coformulation is approved for use in both antiretroviral therapy-naïve and -experienced patients.^[97] In order to improve its oral bioavailability (section 3.1.1), the coformulation should be administered with meals of moderate-to-high fat content.^[14,15]

Lopinavir/ritonavir coformulated capsules and oral solution should be stored refrigerated (at 2–8°C) until dispensed and used within 2 months after reaching room temperature (up to 25°C).^[15]

The drug is indicated for use only in combination with other antiretroviral agents.^[15] When coadministered with either nevirapine or efavirenz (and probably with amprenavir), the dosage of lopinavir/ritonavir should be increased by 33% (i.e. to 533/133mg and 300/75 mg/m², in adults and children [aged <12 years], respectively, twice daily) to achieve therapeutic lopinavir plasma concentrations (section 4.2.1).^[15,55,58,62] Appropriate dosages of amprenavir, saquinavir and indinavir when administered in combination with lopinavir/ritonavir have not yet been established.^[15]

As lopinavir and ritonavir are both metabolised principally by the liver (section 3.3) and the pharmacokinetic properties of the coformulated drugs have not been established in patients with hepatic impairment (e.g. patients with AST/ALT levels >2.5 –^[3,67] or >3 -fold^[68] the ULN were excluded from randomised, double-blind, multicentre clinical trials), the drug should be administered with caution in this patient population.^[15] Since $<3\%$ of the lopinavir dose is excreted unchanged in the urine after multiple-dose administration of lopinavir/rito-

128 36 183

navir (section 3.4), the impact of renal insufficiency on lopinavir elimination is likely to be minimal.

A number of clinically important drug interactions have been reported with lopinavir/ritonavir (section 4), necessitating dosage adjustments of lopinavir/ritonavir and/or the interacting drugs (section 4.2, table III and IV). Several drugs are contraindicated in patients receiving the coformulation (table II and section 4.1).

Data on lopinavir/ritonavir use in pregnant women are currently not available and the drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.^[15] In the US, lopinavir/ritonavir is classified under pregnancy category C.^[15]

Whether lopinavir is secreted in human milk is unknown, although this has been demonstrated in studies in rats.^[15] Nevertheless, HIV-infected mothers receiving lopinavir/ritonavir should not breast-feed to avoid risking both serious adverse reactions in and postnatal transmission of HIV to their nursing infants.^[15]

As increased spontaneous bleeding has been reported in patients with haemophilia A and B receiving PIs (despite the lack of evidence of a causal relationship), caution should be exercised when administering lopinavir/ritonavir to this patient group.^[15]

9. Place of Lopinavir/Ritonavir in the Management of HIV Infection

According to estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the WHO, 37 million adults and 3 million children (aged <15 years) were living with HIV at the end of 2001.^[98] This is >50% higher than the figures projected by WHO in 1991 on the basis of the data then available. In 2001 an estimated 5 million people became infected with HIV-1 and 3 million died from HIV/AIDS globally, despite the use of antiretroviral therapy which reduced HIV-1- and AIDS-related deaths in developed countries.^[98]

The pandemic of HIV-1 infection and its fatal prognosis emphasise the need for effective antiretroviral therapy. The use of agents targeting HIV-1 reverse transcriptase has been limited by the emergence of treatment-limiting toxicities (of both NRTIs and NNRTIs), development of resistant mutants (mostly with NNRTIs) and the inability to provide

adequate long-term suppression of viral replication (NRTIs).^[1]

On the other hand, inhibitors of HIV-1 protease, another essential viral enzyme, can effectively suppress viral replication (decrease the plasma viral load) and induce substantial immune system recovery (increase the CD4+ cell count).^[1] However, their use is generally limited by modest oral bioavailability and short $t_{1/2}$ producing low C_{trough} and requiring frequent administration of high doses (i.e. large number of 'pills') to achieve antiretroviral efficacy *in vivo*. The downside of the latter is development of significant adverse events which, coupled with strict dietary restrictions and the high pill burden of PIs, may compromise patients' adherence to the PI-based treatment regimens.

A variety of antiretroviral drugs, approved by the US FDA, are currently available for the treatment of HIV-1 infection.^[1,99] They are classified according to their mechanism of action as either NRTIs (e.g. abacavir, didanosine, lamivudine, stavudine, tenofovir disoproxil, zalcitabine, zidovudine), NNRTIs (e.g. delavirdine, efavirenz, nevirapine) or PIs (e.g. amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir).^[100] The best treatment results, in terms of both the clinical outcomes and surrogate markers, are achieved with regimens containing three or more antiretroviral drugs.^[50,51] The most commonly recommended triple combination antiretroviral drug regimens include a dual NRTI plus either a PI (PI-triple), an NNRTI (NNRTI-triple) or a third NRTI (triple-NUC).^[101]

Pharmacokinetic enhancement by low-dose ritonavir has been previously shown to produce sustained plasma concentrations of PIs, including lopinavir, in excess of those required to completely (i.e. below LLQ) suppress viral replication.^[42,102-104] This pharmacological 'boost' also reduces the dosage and administration frequency of PIs in combined regimens. Coformulated lopinavir/ritonavir has been developed to maximise these pharmacokinetic benefits and to improve patient compliance by the more convenient (twice-daily) administration regimen, and is available in capsule and liquid formulations.^[15] Coformulated lopinavir/ritonavir is currently regarded as a first-choice agent for the treatment of patients with HIV-1 infection in combination with other antiretroviral agents.^[1]

In the US and Europe, the lopinavir/ritonavir coformulation is approved for use in combination

with other antiretroviral agents for the treatment of HIV-1 infection in both antiretroviral therapy-naïve and -experienced patients (section 8). The optimal lopinavir/ritonavir dose combination is 400/100mg in a twice-daily regimen, administered with moderate-to-high fat content meals (section 3.1.1 and section 8) as determined in single- and multiple-dose pharmacokinetic studies in adults (both healthy volunteers and HIV-1-infected patients).^[4,14,27] The current treatment guidelines^[1] strongly recommend the use of coformulated lopinavir/ritonavir in combination with two NRTIs as a first-line option for the treatment of HIV-1 infection in patients with no or limited prior antiretroviral drug experience.

The effects of lopinavir/ritonavir on primary clinical endpoints of HIV-1 infection (disease progression to AIDS and death) have not yet been studied. However, lopinavir/ritonavir-based triple and quadruple antiretroviral drug regimens provide effective suppression of plasma HIV-1 load (below LLQ) and a sustained immunological response (measured by increasing CD4+ cell counts), as confirmed in randomised, double-blind, multicentre clinical trials in both antiretroviral therapy-naïve and -experienced adults (see section 5.1.1 and 5.1.2, and table V for details) and nonblind trials in 'experienced' adults (section 5.1.2) and children (section 5.2).

Studies comparing the therapeutic efficacy of lopinavir/ritonavir with that of other antiretroviral agents are sparse. In the only comparative phase III study published thus far,^[68,83,84] lopinavir/ritonavir in combination with lamivudine and stavudine showed significantly greater and more durable suppression of viral load than nelfinavir combined with the same two NRTIs (table V and section 5.1.1). Likewise, lopinavir/ritonavir induced significantly greater immune system recovery than nelfinavir, in patients with baseline CD4+ cell counts <50 cell/ μ L. A large, randomised, nonblind, multicentre, phase IV clinical trial is currently underway to compare the efficacy and safety of ritonavir-boosted lopinavir- versus saquinavir-based treatment regimens in HIV-1-infected patients ($n = 326$) who are naïve or experienced to prior PI use.^[105] Comparative studies of ritonavir-boosted PIs (including lopinavir/ritonavir) versus NNRTIs would further aid decisions in selecting the best regimens for the treatment of HIV-1 infection.

The lopinavir/ritonavir-based PI-triple regimens appear to have greater potential for long-term suc-

cess in the treatment of antiretroviral therapy-naïve HIV-1-infected patients than other triple combination antiretroviral regimens (i.e. other PI-triple, NNRTI-triple and triple-NUC). A systematic review^[101] of 23 clinical trials, involving 19 such triple regimens in 3257 antiretroviral therapy-naïve patients, estimated that, after 48 weeks of treatment, 45–51% of enrolled patients would still have plasma HIV-1 RNA levels ≤ 50 copies/mL, whereas, for the same timepoint and level of suppression, the lopinavir/ritonavir-based triple regimens are generally effective in 67–100% (ITT analysis)^[3,68] of 'naïve' patients with similar baseline characteristics (e.g. median plasma viral load and CD4+ cell count^[68,80]). This high level of viral suppression in 'naïve' patients has been maintained with the lopinavir/ritonavir-based triple regimen even after 4 years of therapy (section 5).^[17]

Thus far, the emergence of resistance to antiretroviral agents, including PIs, has been one of the greatest obstacles to the successful long-term treatment of HIV-1 infection. Incomplete suppression of viral replication during therapy fosters the emergence of resistant virus strains, leading to a resurgence of high-level replication and virological failure. Improved suppression of viral replication (i.e. achieved more rapidly and sustained for longer time) by the lopinavir/ritonavir-based regimens appears to prevent or delay development of drug resistance to lopinavir and cross-resistance to other PIs. This is reflected in the absence and low percentage of mutant HIV-1 strains with resistance to coformulated lopinavir/ritonavir in antiretroviral therapy-naïve and -experienced patients, respectively, to date (section 2.3). However, these observations await further confirmation from long-term studies that will incorporate HIV-1 genotyping at baseline.

Lopinavir/ritonavir-based regimens have demonstrated better virological response in patients harbouring HIV-1 with five or less PI mutations than in patients carrying HIV-1 with more than five PI mutations associated with reduced susceptibility to lopinavir (section 2.3.2 and 2.3.2).^[20,23,24] This suggests that five PI resistance mutations represents the point at which clinically relevant reduction of sensitivity to lopinavir begins to occur.^[23,24] The correlation of virological response to baseline lopinavir phenotype and mutation score observed in these studies suggests that baseline genotype and/or phenotype testing may be beneficial in optimising the use of the lopinavir/ritonavir coformulation for

the treatment of HIV-1 infection in PI-experienced patients.

The lopinavir/ritonavir-based triple regimens appear to be equally effective in women and men with HIV-1 infection (section 5.1.1).^[86] This is important as recent reports indicate a dramatic rise in HIV-1 infection rates in women worldwide.^[106] According to the UNAIDS, almost one-third of all *de novo* acquired infections in the US now occur in women.^[107]

Similarly, the baseline hepatitis B/C status of HIV-positive adults (both men and women) does not appear to modify the effectiveness (section 5.1.1 and table VI) or overall tolerability (section 6.1.1) of the lopinavir/ritonavir-based PI triple regimens. However, treatment should be administered with caution in patients with hepatic impairment,^[15] as both lopinavir and ritonavir are metabolised principally in the liver (section 3.3) and their pharmacokinetic properties in this patient population are not yet established (section 3.5 and 8).

A number of clinically important drug interactions have been reported with lopinavir/ritonavir (section 4), necessitating dosage adjustments of lopinavir/ritonavir and/or the interacting drugs (section 4.2, table III and IV). Several drugs are contraindicated in patients receiving the coformulation (table II and section 4.1).

Intravenous use of illicit drugs and 'needle-sharing', is frequent among HIV-positive individuals and represents the second most common route of HIV-1 infection transmission globally (estimated 5–10% of total HIV transmissions).^[108] The methadone maintenance programmes are a form of treatment of opioid abuse and dependence. Recent reports^[45,66] suggested that lopinavir/ritonavir could be the preferred antiretroviral agent for use in HIV-1-infected patients participating in these programmes because the coformulation neither changes the methadone dosage requirements nor precipitates opioid withdrawal symptoms (unlike nevirapine^[109–111] and efavirenz^[111]) [section 4.2.2].

Mycobacterial tuberculosis is an AIDS-defining condition in patients with laboratory evidence of HIV-1.^[108] Coadministration of the antimycobacterial agent rifampicin with lopinavir/ritonavir at standard dosages is not recommended because of pharmacokinetic interactions leading to subtherapeutic lopinavir exposure and possible development of resistance (see section 4.1 for details). How-

ever, appropriate lopinavir/ritonavir dosage adjustment (section 4.1) in conjunction with therapeutic drug monitoring may permit concurrent use of rifampicin for the treatment of tuberculosis in patients with HIV-1 infection.

Antiretroviral therapy can be used to effectively decrease levels of HIV-1 RNA in both plasma and the anatomical sanctuary sites such as the genital tract^[112,113] and CSF,^[114] which have been described as viral reservoirs.^[115–117] However, unlike other PIs such as indinavir^[36,114] and amprenavir,^[118] both lopinavir (section 3.2) and ritonavir^[119] penetrate poorly from the bloodstream into the seminal plasma or cervicovaginal secretions, allowing for incomplete suppression of viral replication and development of resistant viral strains in these body compartments. Consequently, the presence of resistant HIV-1 strains in the genital tract presents a risk to both the patient (from systemic virological failure through re-infection with HIV-1 strains resistant to current therapy) and his/her sexual partner(s) [of acquiring an infection with an HIV-1 strain that is potentially more difficult to treat].^[112,115] It is, therefore, necessary to combine lopinavir/ritonavir with antiretroviral drugs known to penetrate well into the human genital tract (the NRTIs zidovudine,^[120,121] lamivudine,^[121,122] stavudine^[122] and abacavir;^[123] the NNRTIs nevirapine^[122] and efavirenz;^[124] or the PIs indinavir^[34,36,114] and amprenavir^[118]). Penetration of lopinavir and ritonavir into CSF also appears to be very low (section 3.2).

In phase II/III clinical trials, lopinavir/ritonavir was well tolerated as indicated by the low rates of drug-related therapy discontinuations in both antiretroviral therapy-naïve and -experienced patients (table IX). This is in contrast to 'high-dose' ritonavir, which has the highest adverse event-related drug discontinuation rate among PIs.^[125] The tolerability profile of lopinavir/ritonavir may be preferable to that of indinavir, which is associated with nephrolithiasis,^[126] and is very similar to that of nelfinavir (table IX), except for the higher incidence of grade 3/4 triglycerides elevation observed with the coformulation in antiretroviral therapy-naïve patients (section 6.1.1). The coformulation appears to be associated with marked hypertriglyceridaemia and hypercholesterolaemia more frequently in patients failing prior treatment with multiple PIs than in antiretroviral therapy-naïve patients, as well as in patients with elevated baseline triglycerides and cholesterol levels (section 6.1.1 and table IX). The

clinical significance of these lipid abnormalities, which have been associated with the use of PIs in general, lies in their predisposition for development of cardiovascular events and pancreatitis.^[1] Therefore, treatment with lopinavir/ritonavir should be accompanied by monitoring for lipid abnormalities and may require cautious use of lipid-lowering agents (see section 4.1 and 4.2.2 for possible drug interactions with the coformulation).

As with other PIs,^[1] the most common adverse events in adults, of at least moderate severity, associated with lopinavir/ritonavir are GI disturbances (diarrhoea being the most frequently reported) [table IX and section 6.1]. The other common adverse events (asthenia, headache and skin rash) tend to occur less frequently with lopinavir coformulated with 'low-dose' ritonavir (table IX) than with 'high-dose' ritonavir alone.^[127,128] Circumoral paraesthesia, a common adverse event and a cause of treatment discontinuation with 'high-dose' ritonavir,^[127,128] is not observed with the lopinavir/ritonavir coformulation.

In children, the incidence of adverse events associated with lopinavir/ritonavir of at least moderate severity appears to be low (section 6.2). In both adult and paediatric populations, serious adverse events (such as pancreatitis, myocardial infarction, lactic acidosis and hepatic failure) [section 6.1.2 and 6.2] have occurred infrequently during lopinavir/ritonavir therapy.

The use of PI drugs in the treatment of HIV-1 infection has been associated with development of lipid abnormalities (elevated serum cholesterol and triglyceride levels) as well as metabolic disorders including insulin resistance and diabetes mellitus, body fat redistribution (lipodystrophy), and cardiovascular disorders such as myocardial infarction.^[129-137] Lipodystrophy is of particular concern as many patients become reluctant to accept treatment with PIs because of their potential to induce cosmetic changes in body shape (e.g. loss of fat from the face and limbs, accumulation of visceral fat in the abdomen, breast enlargement and occasional formation of a 'buffalo hump').^[129-131,135,138] Development of Cushingoid appearance thus becomes an obvious stigma of HIV-1 infection and the antiretroviral treatment received for it. Changes in body fat composition have been observed in a small percentage of adult antiretroviral therapy-naïve patients (7% over 60 weeks; section 6.1) receiving lopinavir/

ritonavir-based treatment. However, it is possible that these findings may differ with wider clinical experience, as effects of disturbances in lipid metabolism tend to develop over time and should be actively monitored.

The cost effectiveness of the PI- and NNRTI-triple therapies in the management of HIV-1 infection have been previously well established (in comparison with no antiretroviral therapy or with mono-, dual- and triple-NUC therapies) in the US, Europe and Canada.^[139-141] Pharmacoeconomic data on lopinavir/ritonavir use in the treatment of HIV-1 infection are limited but the available analyses suggest a cost savings with its use in comparison with nelfinavir (section 7).

Although the acquisition costs of particular drugs may vary, coformulated lopinavir/ritonavir maintains the potential advantage of low 'pill burden' and 'single-pill' administration over the other PIs. At the recommended dosage for adults and adolescents (section 8) coformulated lopinavir/ritonavir is administered as three capsules twice daily. In contrast, recommended regimens of other PIs range from 5–8 capsules or tablets twice daily^[127,142,143] to 2–6 capsules three times per day.^[126,143,144] Daily pill burden of lopinavir/ritonavir (six capsules) compares favourably with those of saquinavir^[145,146] and amprenavir^[142,147] (eight capsules each) but less favourably with indinavir (four capsules),^[148-150] in most clinically accepted regimens for PIs coadministered with a 'low-dose' ritonavir. The low pill burden of lopinavir/ritonavir is expected to improve adherence to the treatment regimen,^[29] whereas its administration in coformulated capsules eliminates the possibility that patients may take the active PI (lopinavir) without its pharmacokinetic enhancer (ritonavir). Consequently, administration of lopinavir/ritonavir in the same capsule reduces the risk of subtherapeutic lopinavir plasma concentrations and the possible development of viral resistance.

Like all other available therapies, lopinavir/ritonavir is, however, not a cure for AIDS and patients treated with this drug may still continue to develop illnesses associated with advanced HIV-1 infection, including opportunistic infections. Lopinavir/ritonavir has also not been shown to reduce the risk of transmission of HIV-1 infections to others through sexual contact or blood contamination.^[15] The safety and efficacy of lopinavir/ritonavir have not yet been studied in pregnant women and neonates.

In conclusion, coformulated lopinavir/ritonavir is a novel PI that, in combination with other antiretroviral agents, suppresses plasma viral load and enhances immunological status in therapy-naïve and -experienced patients with HIV-1 infection. Lopinavir/ritonavir appears equally effective in adults and children and in both sexes, although data in children are limited, and more effective than nelfinavir in antiretroviral therapy-naïve patients. The coformulation is also suitable for 'salvage' therapy, because of its high barrier to development of resistance. Given its clinical efficacy, a tolerability profile in keeping with this class of drugs, a favourable resistance profile and easy-to-adhere-to administration regimen, coformulated lopinavir/ritonavir should be regarded as a first-line option when including a PI in the management of HIV-1 infection.

References

1. HIV/AIDS Treatment Information Service. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents [online]. Available from URL: <http://www.hivatis.org> [Accessed 2003 Mar 7]
2. Sham HL, Kempf DJ, Molla A, et al. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. *Antimicrob Agents Chemother* 1998; 42 (12): 3218-24
3. Murphy RL, Brun S, Hicks C, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results. *AIDS* 2001 Jan 5; 15 (1): F1-9
4. Bertz R, Lam W, Brun S, et al. Multiple-dose pharmacokinetics (PK) of ABT-378/ritonavir (ABT/r) in HIV+ subjects [abstract plus poster no. 0327]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco (CA), 16
5. Hurst M, Faulds D. Lopinavir. *Drugs* 2000 Dec; 60 (6): 1371-9
6. Debouck C. The HIV-1 protease as a therapeutic target for AIDS. *AIDS Res Hum Retroviruses* 1992; 8 (2): 153-64
7. De Clercq E. New developments in anti-HIV chemotherapy. *Biochim Biophys Acta* 2002 Jul 18; 1587 (2-3): 258-75
8. Henderson LE, Bowers MA, Sowder RC, et al. Gag proteins of the highly replicative MN strain of human immunodeficiency virus type 1: posttranslational modifications, proteolytic processing, and complete amino acid sequences. *J Virol* 1992 Apr; 66 (4): 1856-65
9. Kohl NE, Emini EA, Schleif WA, et al. Active human immunodeficiency virus protease is required for viral infectivity. *Proc Natl Acad Sci USA* 1988 Jul; 85: 4686-90
10. Roberts NA, Martin JA, Kinchington D, et al. Rational design of peptide-based HIV proteinase inhibitors. *Science* 1990 Apr 20; 248: 358-61
11. Overton HA, McMillan DJ, Gridley SJ, et al. Effect of two novel inhibitors of the human immunodeficiency virus protease on the maturation of the HIV gag and gag-pol polyproteins. *Virology* 1990 Nov; 179: 508-11
12. Molla A, Vasavanonda S, Kumar G, et al. Human serum attenuates the activity of protease inhibitors toward wild-type and mutant human immunodeficiency virus. *Virology* 1998 Oct 25; 250: 255-62
13. Molla A, Vasavanonda S, Denissen J, et al. Effect of human serum proteins on the antiretroviral activity of ritonavir and ABT-378, potent inhibitors of HIV protease [abstract]. 4th Conference on Retroviruses and Opportunistic Infections; 1997 Jan 22-26; Washington, DC.
14. Gustavson L, Lam W, Bertz R, et al. Assessment of the bioequivalence and food effects for liquid and soft elastic capsule formulations of ABT-378/ritonavir (ABT-378/r) in healthy subjects [poster]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto
15. Abbott Laboratories. Kaletra™ (lopinavir/ritonavir) capsules and oral solution. Product label information. Abbott Laboratories, North Chicago, IL [online]. Available from URL: <http://www.kaletra.com> [Accessed 2002 Oct 2]
16. Boulmé R, Dugas O, Halfon P, et al. Analysis of mutational patterns associated with resistance to tenofovir DF and lopinavir/ritonavir [poster no. 352]. 8th European Conference on Clinical Aspects and Treatment of HIV-Infection; 2001 Oct 28-31; Athens
17. Murphy R, Brun S, King M, et al. Lopinavir/ritonavir (Kaletra) in antiretroviral-naïve HIV+ patients: 4-year follow-up [abstract plus poster no. H-165]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 Sep 27; San Diego (CA), 261
18. Bernstein B, Kempf D, King M, et al. Comparison of the emergence of resistance in a blinded phase III study with Kaletra™ (lopinavir/ritonavir) or nelfinavir plus d4T/3TC from week 24 through 96 [abstract no. I-1768 plus poster]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Sep 22-25; Chicago (IL), 338
19. Clumeck N, Brun S, Sylte J, et al. Kaletra (ABT-378/r) and efavirenz: one-year safety/efficacy evaluation and phenotypic breakpoints in multiple-PI-experienced patients [abstract no. 525]. 8th Conference on Retroviruses and Opportunistic Infections; 2001 Feb 4; Chicago (IL)
20. Danner S, Brun S, Richards B, et al. Kaletra (lopinavir/ritonavir) and efavirenz: 72-week safety and efficacy evaluation in multiple PI-experienced patients [poster no. 1925]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Dec; Chicago (IL)
21. Kempf DJ, Isaacson JD, King MS, et al. Analysis of the virologic response with respect to baseline viral phenotype and genotype in protease inhibitor-experienced HIV-1-infected patients receiving lopinavir/ritonavir. *Antiviral Ther* 2002 Sep; 7 (3): 165-74
22. Kempf DJ, Isaacson JD, King MS, et al. Identification of genotypic changes in human immunodeficiency virus protease that correlate with reduced susceptibility to the protease inhibitor lopinavir among viral isolates from protease inhibitor-experienced patients. *J Virol* 2001 Aug; 75 (16): 7462-9
23. de Mendoza C, Martin-Carbonero L, Barreiro P, et al. Salvage treatment with lopinavir/ritonavir (Kaletra) in HIV-infected patients failing all current antiretroviral drug families. *HIV Clin Trials* 2002 Jul-Aug; 3 (4): 304-9
24. Calvez V, Cohen-Codar I, Marcelin AG, et al. Efficacy of lopinavir/ritonavir in 104 multiple PI-experienced patients according to mutational patterns: data from the French ATU program [abstract no. 234 plus poster]. 8th European Conference on Clinical Aspects and Treatment of HIV-Infection; 2001 Oct 28-31; Athens, 154
25. Ngo Van P, Cohen-Codar I, Boer F, et al. Study of the initial response to Kaletra® in HIV treatment-experienced patients: the ATU pre-registrational cohort in France [abstract no. P236 plus poster]. 8th European Conference on Clinical Aspects and Treatment of HIV-Infection; 2001 Oct 28-31; Athens, 155
26. Cahn P, Renz C, Saez-Llorens X, et al. Kaletra™ (ABT-378/ritonavir) in HIV-infected children at 72 weeks [poster]. 1st International AIDS Society Conference; 2001 Jul 8-11; Buenos Aires
27. Lal R, Hsu A, Granneman GR, et al. Multiple dose safety, tolerability and pharmacokinetics of ABT-378 in combination with ritonavir [abstract no. 647]. 5th Conference on Retroviruses and Opportunistic Infections; 1998 Feb 1-5; Chicago (IL)

A service of the U.S. National Library of Medicine
and the National Institutes of HealthMy NCBI [?] 180
[Sign In] [Register]All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Books
Search PubMed for [] Go Clear Advanced Search

Limits Preview/Index History Clipboard Details

Display AbstractPlus Show 20 Sort By Send to

All: 1 Review: 0

1: N Engl J Med. 2002 Jun 27;346(26):2039-46.

Click here to read Links

Comment in:

N Engl J Med. 2002 Jun 27;346(26):2022-3.

Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection.

Walmsley S, Bernstein B, King M, Arribas J, Beall G, Ruane P, Johnson M, Johnson D, Lalonde R, Japour A, Brun S, Sun E; M98-863 Study Team.Toronto Hospital, University Health Network, University of Toronto, Toronto, ON, Canada.
sharon.walmsley@uhn.on.ca

BACKGROUND: Lopinavir is a newly developed inhibitor of human immunodeficiency virus (HIV) protease that, when formulated with ritonavir, yields mean trough plasma lopinavir concentrations that are at least 75 times as high as that needed to inhibit replication of wild-type HIV by 50 percent.

METHODS: We conducted a double-blind trial in which 653 HIV-infected adults who had not received antiretroviral therapy for more than 14 days were randomly assigned to receive either lopinavir-ritonavir (400 mg of lopinavir plus 100 mg of ritonavir twice daily) with nelfinavir placebo or nelfinavir (750 mg three times daily) with lopinavir-ritonavir placebo. All patients also received open-label stavudine and lamivudine. The primary efficacy end points were the presence of fewer than 400 HIV RNA copies per milliliter of plasma at week 24 and the time to the loss of virologic response through week 48. **RESULTS:** At week 48, greater proportions of patients treated with lopinavir-ritonavir than of patients treated with nelfinavir had fewer than 400 copies of HIV RNA per milliliter (75 percent vs. 63 percent, $P < 0.001$) and fewer than 50 copies per milliliter (67 percent vs. 52 percent, $P < 0.001$). The time to the loss of virologic response was greater in the lopinavir-ritonavir group than in the nelfinavir group (hazard ratio, 2.0; 95 percent confidence interval, 1.5 to 2.7; $P < 0.001$). The estimated proportion of patients with a persistent virologic response through week 48 was 84 percent for patients receiving lopinavir-ritonavir and 66 percent for those receiving nelfinavir. Both regimens were well tolerated, with the rate of discontinuation related to the study drugs at 3.4 percent among patients receiving lopinavir-ritonavir and 3.7 percent among patients receiving nelfinavir. Among patients with more than 400 copies of HIV RNA per milliliter at some point from week 24 through week 48, resistance mutations in HIV protease were demonstrated in viral isolates from 25 of 76 nelfinavir-treated patients (33 percent) and none of 37 patients treated with lopinavir-ritonavir ($P < 0.001$). **CONCLUSIONS:** For the initial treatment of HIV-infected adults, a combination regimen that includes lopinavir-ritonavir is well tolerated and has antiviral activity superior to that of a nelfinavir-containing regimen.

PMID: 12087139 [PubMed - indexed for MEDLINE]

Related Articles

Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. [JAMA. 2000]

Review Lopinavir/ritonavir: a review of its use in the management of HIV infection. [Drugs. 2003]

Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. Infect Dis. 2004]

Baseline HIV-1 RNA level and CD4 cell count predict time to loss of virologic response to nelfinavir, but not lopinavir/ritonavir, in antiretroviral therapy-naïve patients. [Drugs. 2003]

Review Nelfinavir. A review of its therapeutic efficacy in HIV infection. [Drugs. 1998]

» See Reviews... | » See All...

Patient Drug Information

Lamivudine (Epivir®, Epivir-HBV®, Combivir® (as a combination product containing Lamivudine and Zidovudine), ...) Lamivudine (Epivir) is used in combination with other medications to treat human immunodeficiency virus (HIV) infection in patients with acquired immunodeficiency syndrome (AIDS). Lamivudine is not a cure and may not dec...

» read more ...

Ritonavir (Norvir®, Norvir® Softgel) Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

» read more ...

Stavudine (Zerit®) Stavudine is used in combination with other antiviral medications to treat human immunodeficiency virus (HIV) infection in patients with or without acquired immunodeficiency syndrome (AIDS). Stavudine is in a class of an...

» read more ...

» See all 5 Drug Reports...

Display AbstractPlus Show 20 Sort By Send to

Write to the Help Desk

NCBI | NLM | NIH

Department of Health & Human Services

Privacy Statement | Freedom of Information Act | Disclaimer

A service of the U.S. National Library of Medicine
and the National Institutes of HealthMy NCBI
(Sign In) (Register)All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Books
Search PubMed for [Advanced Search](#)

Limits Preview/Index History Clipboard Details

Display AbstractPlus 20 All: 1 ☐ AIDS. 2002 Oct 18;16(15):2081-3.☒ [Click here to read](#) [Links](#)**Clinical use of lopinavir/ritonavir in a salvage therapy setting: pharmacokinetics and pharmacodynamics.****Boffito M, Arnaudo I, Raiteri R, Bonora S, Sinicco A, Di Garbo A, Reynolds HE, Hoggard PG, Back DJ, Di Perri G**

Department of Infectious Diseases, University of Torino, Turin, Italy.

Lopinavir/ritonavir was administered to 35 HIV-infected patients after therapeutic failure with other protease inhibitors. The pharmacokinetics (trough concentrations) and baseline viral genotype were determined, together with the immunovirological outcome. The 22 responders had significantly higher mean lopinavir concentrations and lower baseline numbers of mutations. On multivariate analysis, a lopinavir concentration of 5.7 microg/ml or greater was an independent predictor of viral suppression over a 9-month follow-up period.

PMID: 12370509 [PubMed - indexed for MEDLINE]

Related Articles

Human immunodeficiency virus type 1 genotypic and pharmacokinetic determinants of the virological response to lopinavir-ritonavir-containing therapy in protease inhibitor-experienced patients. *Anticancer Agents Chemother.* 2002

Prediction of virological response to lopinavir/ritonavir using the genotypic inhibitory quotient. *Anticancer Agents Chemother.* 2004

Virological, intracellular and plasma pharmacological parameters predicting response to lopinavir/ritonavir (KALEPHAR study). *[AIDS. 2004]*

Review Lopinavir/ritonavir: a review of its use in the management of HIV infection. *[Drugs. 2003]*

Review Lopinavir/ritonavir in the treatment of human immunodeficiency virus infection. *[Anticancer Agents Chemother. 2005]*

[See Reviews...](#) [See All...](#)**Patient Drug Information**

Ritonavir (Norvir®, Norvir® Softgel) Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

[read more...](#)

Lopinavir and Ritonavir (Kaletra®) The combination of lopinavir and ritonavir is used with other antiviral medications to treat human immunodeficiency virus (HIV) in patients with acquired immunodeficiency syndrome (AIDS). Lopinavir is in a class of medic...

[read more...](#)Display AbstractPlus 20 [Write to the Help Desk](#)[NCBI](#) | [NLM](#) | [NIH](#)[Department of Health & Human Services](#)[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

A service of the U.S. National Library of Medicine
and the National Institutes of HealthMy NCBI
[Sign In] [Register]All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Books
Search PubMed for [Advanced Search](#)[Limits](#) [Preview/index](#) [History](#) [Clipboard](#) [Details](#)Display [AbstractPlus](#) 20 ☐ 1: [Pediatr Infect Dis J. 2003 Mar;22\(3\):216-24.](#)☒ [Click here to read](#) [Links](#)**Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children.****Sáez-Llorens X, Violari A, Deetz CO, Rode RA, Gomez P, Handelsman E, Pelton S, Ramilo O, Cahn P, Chadwick E, Allen U, Arpadi S, Castrejon MM, Heuser RS, Kempf DJ, Bertz RJ, Hsu AF, Bernstein B, Renz CL, Sun E.**

Hospital del Niño, Panama City, Panama. xsaezli@cwpanama.net

BACKGROUND: Lopinavir/ritonavir has demonstrated antiviral activity in the HIV-infected adult. **SUBJECTS:** The objective of this study was to investigate a liquid coformulation of lopinavir/ritonavir, in combination with reverse transcriptase inhibitors, in HIV-infected children. **METHODS:** One hundred antiretroviral (ARV)-naïve and ARV-experienced, nonnucleoside reverse transcriptase inhibitor-naïve children between 6 months and 12 years of age participated in this Phase I/II, open label, multicenter trial. Subjects initially received either 230/57.5 mg/m² or 300/75 mg/m² lopinavir/ritonavir twice daily; ARV-naïve subjects also received stavudine and lamivudine, whereas ARV-experienced subjects also received nevirapine and one or two nucleoside reverse transcriptase inhibitors. Lopinavir/ritonavir pharmacokinetics, safety and efficacy were evaluated. **RESULTS:** All subjects were escalated to the 300/75 mg/m² twice daily dose based on results from an interim pharmacokinetic and safety evaluation. The pharmacokinetics of lopinavir did not appear to be dependent on age when dosing was based on body surface area but were decreased on coadministration with nevirapine. Overall 79% of subjects had HIV RNA levels <400 copies/ml at Week 48 (intent-to-treat: missing = failure). Mean increases in absolute and relative (percent) CD4 counts from baseline to Week 48 were observed in both ARV-naïve subjects (404 cells/mm³; 10.3%) and ARV-experienced subjects (284 cells/mm³; 5.9%). Only one subject prematurely discontinued the study because of a study drug-related adverse event. **CONCLUSIONS:** The liquid coformulation of lopinavir/ritonavir demonstrated durable antiviral activity and was safe and well-tolerated after 48 weeks of treatment in HIV-infected children.

PMID: 12634581 [PubMed - indexed for MEDLINE]

Related Articles*Review* Lopinavir/ritonavir: a review of its use in the management of HIV infection. [Drugs. 2003]

Safety and antiviral response at 12 months of lopinavir/ritonavir therapy in human immunodeficiency virus-1-infected children experienced with three classes of antiretrovirals. [Pediatr Infect Dis J. 2005]

Interactions between amprenavir and the lopinavir-ritonavir combination in heavily pretreated patients infected with human immunodeficiency virus [Clin Pharmacol Ther. 2004]

Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. [Pediatr Infect Dis J. 2005]

Review Lopinavir/ritonavir in the treatment of human immunodeficiency virus infection [Expert Opin Pharmacother. 2005]

» See Reviews... | » See All...

Patient Drug Information

Lamivudine (Epivir®, Epivir-HBV®, Combivir® (as a combination product containing Lamivudine and Zidovudine), ...) Lamivudine (Epivir) is used in combination with other medications to treat human immunodeficiency virus (HIV) infection in patients with acquired immunodeficiency syndrome (AIDS). Lamivudine is not a cure and may not dec...

» read more ...

Ritonavir (Norvir®, Norvir® Softgel) Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

» read more ...

Nevirapine (Viramune®) Nevirapine is used in combination with other medications to treat human immunodeficiency virus (HIV) infection in patients with or without acquired immunodeficiency syndrome (AIDS). Nevirapine is in a class of medication..

» read more ..

» See all 5 Drug Reports ...

Display [AbstractPlus](#) 20 [Write to the Help Desk](#)[NCBI](#) | [NLM](#) | [NIH](#)[Department of Health & Human Services](#)[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

A service of the U.S. National Library of Medicine
and the National Institutes of HealthMy NCBI
[Sign In] [Register]All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Books
Search PubMed for Go Clear Advanced Search

Limits Preview/Index History Clipboard Details

Display AbstractPlus Show 20 Sort By Send to
All: 1 Review: 0

1: AIDS. 2004 Mar 26;18(5):775-9.

Click here to read Links

Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naïve patients: 4 year follow-up study.**Hicks C, King MS, Gulick RM, White AC Jr, Eron JJ Jr, Kessler HA, Benson C, King KR, Murphy RL, Brun SC.**

Duke University Medical Center, Durham, North Carolina, 27710, USA.

OBJECTIVE: Combination antiretroviral therapy with lopinavir/ritonavir (LPV/r) has been highly effective in clinical trials. Results of long-term therapy with LPV/r-based regimens have not been previously reported. This study describes the 4-year (204-week) safety and antiretroviral activity of LPV/r-based treatment in antiretroviral-naïve individuals. **DESIGN:** Long-term, open-label follow-up of a phase II, prospective, randomized, multicenter trial. **METHODS:** A group of 100 antiretroviral-naïve HIV-infected patients were randomized to one of three blinded doses of LPV/r [200/100 mg (n = 16), 400/100 mg (n = 51), or 400/200 mg (n = 33)] with stavudine 40 mg and lamivudine 150 mg every 12 hours. After 48 weeks, LPV/r was dosed open-label at 400/100 mg every 12 hours with stavudine and lamivudine. **RESULTS:** Mean baseline plasma HIV-1 RNA and CD4 cell count were 4.9 log₁₀ copies/ml and 338 x 10 cells/l, respectively. At week 204, 72 patients remained on study, 70 of whom had HIV-1 RNA < 50 copies/ml (70% by intent-to-treat analysis). Twenty-eight patients discontinued therapy prior to week 204 because of adverse events (n = 10), lost to follow-up (n = 9), or other reasons (n = 9). Of 15 patients who met protocol-defined criteria for virologic failure, seven remained on the study regimen and their HIV-1 RNA was re-suppressed to < 50 copies/ml at week 204. Genotypic analysis of rebound viral isolates was available from 10 patients, including all eight patients who discontinued the study prematurely. No isolate demonstrated primary or active site mutations in protease. The most common adverse events were gastrointestinal symptoms and lipid elevations. **CONCLUSIONS:** LPV/r-based therapy provides durable antiretroviral response and is generally well tolerated through 204 weeks of therapy.

PMID: 15075512 [PubMed - indexed for MEDLINE]

Related Articles

Seven-year efficacy of a lopinavir/ritonavir-based regimen in antiretroviral-naïve HIV-1-infected patients. [AIDS. 2008]

ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results. [AIDS. 2001]

Efficacy and safety of Indinavir/ritonavir 400/100 mg twice daily plus two nucleoside analogues in treatment-naïve HIV-1-infected patients with CD4+ T-cell counts <200 cells/mm³: 96-week outcomes. [Antivir Ther. 2005]

Review Lopinavir/ritonavir: a review of its use in the management of HIV infection. [Drugs. 2003]

Review Lopinavir/ritonavir: a protease inhibitor for HIV-1 treatment. [Expert Opin Pharmacother. 2005]

» See Reviews... | » See All...

Patient Drug Information

Lamivudine (Epivir®, Epivir-HBV®, Combivir® (as a combination product containing Lamivudine and Zidovudine), ...) Lamivudine (Epivir) is used in combination with other medications to treat human immunodeficiency virus (HIV) infection in patients with acquired immunodeficiency syndrome (AIDS). Lamivudine is not a cure and may not dec...

» read more ...

Ritonavir (Norvir®, Norvir® Softgel) Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

» read more ...

Stavudine (Zerit®) Stavudine is used in combination with other antiviral medications to treat human immunodeficiency virus (HIV) infection in patients with or without acquired immunodeficiency syndrome (AIDS). Stavudine is in a class of an...

» read more ...

» See all 4 Drug Reports...

Display AbstractPlus Show 20 Sort By Send to

Write to the Help Desk

NCBI | NLM | NIH

Department of Health & Human Services

Privacy Statement | Freedom of Information Act | Disclaimer

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 December 2002 (05.12.2002)

PCT

(10) International Publication Number
WO 02/096395 A1

- (51) International Patent Classification⁷: A61K 9/48, 31/513, 31/427, A61P 31/18
- (21) International Application Number: PCT/US02/15955
- (22) International Filing Date: 21 May 2002 (21.05.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/866,285 25 May 2001 (25.05.2001) US
- (71) Applicant: ABBOTT LABORATORIES [US/US];
D-377 AP6D, 100 Abbott Park Road, Abbott Park, IL
60064-6050 (US).
- (72) Inventors: PETRICONI, Sergio; Via Roma 10, I-00042
Anzio (IT). BARBATO, Alessandro; Via Acaia 24,
I-00183 Rome (IT). SCUPPA, Roberta; Via Cagliari 53,
I-04011 Aprilia (Latina) (IT). SALEKI-GERHARDT,
Azita; 1113 Virginia Avenue, Libertyville, IL 60048 (US).
URCH, Martin; 5233-E Oscar Court, Gurnee, IL 60031
(US).
- (74) Agents: CROWLEY, Steven, R. et al.; D-377 AP6D, 100
Abbott Park Road, Abbott Park, IL 60064-6050 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN,
YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/096395 A1

(54) Title: SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR

(57) Abstract: A soft elastic capsule is described containing a pharmaceutical agent or a mixture of pharmaceutical agents. The soft elastic capsule is prepared from a fill composition and a shell composition that impart acceptable physical characteristics to the soft elastic capsule when in an equilibrium state. The pharmaceutical agents of the fill composition are also soluble when the soft elastic capsule is in the equilibrium state.

46
193

WE CLAIM:

1. A soft elastic capsule having a fill and a shell, the fill comprising:
a pharmaceutical agent or combination of pharmaceutical agents,
an alcohol,
a fatty acid, and
the shell comprising:
gelatin, and
at least one plasticizing agent,
wherein said shell has an initial state and an equilibrium state, wherein said initial state shell is underplasticized and said fill contains an alcohol amount in excess of an alcohol amount necessary to solubilize said pharmaceutical agent and said alcohol is not present in the initial state shell composition, and wherein said equilibrium state said shell becomes plasticized by the alcohol from said fill to provide suitable capsule hardness and said fill retains sufficient alcohol to maintain said pharmaceutical agent in solution.
2. The soft elastic capsule of claim 1 wherein the amount of alcohol present in said fill in initial state is in the range of 100-200% greater than the amount necessary to solubilize said pharmaceutical agent.
3. The soft elastic capsule of claim 1 wherein a portion in the range of 40-50% of the amount of alcohol present in said fill in initial state migrates into the shell upon equilibrium state.
4. The soft elastic capsule of claim 1 wherein said pharmaceutical agent comprises a solubilized HIV inhibiting compound or a combination of solubilized HIV inhibiting compounds.
5. The soft elastic capsule of claim 4 wherein said HIV inhibiting compound is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-N-((2-isopropyl-4-thiazolyl)- methyl)amino)carbonyl)-L-

194

valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

6. The soft elastic capsule of claim 4 wherein said combination of solubilized HIV inhibiting compounds is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane (lopinavir).
7. The soft elastic capsule of claim 4 wherein said solubilized HIV inhibiting compound or said combination of solubilized HIV inhibiting compounds is present in said fill in a range of 10-35% by weight.
8. The soft elastic capsule of claim 1 wherein said alcohol is propylene glycol or ethanol.
9. The soft elastic capsule of claim 8 wherein propylene glycol or ethanol are present in said fill in initial state in a range of 3-20% by weight.
10. The soft elastic capsule of claim 1 wherein said alcohol concentration in the fill decreases by not more than 20% after reaching said equilibrium state.
11. The soft elastic capsule of claim 10 wherein after reaching said equilibrium state said shell has acceptable physical characteristics.
12. The soft elastic capsule of claim 11 wherein the acceptable physical characteristics of said shell comprise
 - a hardness in the range of about 4.5 to about 9 Newtons,
 - a total weight of said capsule within 95% of initial weight of capsule and total weight of said fill within 85% of initial weight of said fill,
 - a moisture content of not more than 2% of said fill weight of said capsule,

a disintegration time of not more than 30 minutes, and
an alcohol concentration of at least 40 mg per gram of said fill.

13. The soft elastic capsule of claim 1 wherein said fatty acid is oleic acid.
14. The soft elastic capsule of claim 13 wherein said oleic acid is present in said fill composition in initial state in the range of 50-80% by weight.
15. The soft elastic capsule of claim 1 wherein said fill further comprises a surfactant.
16. The soft elastic capsule of claim 15 wherein said surfactant is Polyoxyl 35 castor oil (Cremophor EL[®]).
17. The soft elastic capsule of claim 15 wherein said surfactant is present in the range of 0-10% by weight of the fill.
18. The soft elastic capsule of claim 1 wherein the gelatin in said capsule is present in the range of 30-60 % by weight of the shell.
19. The soft elastic capsule of claim 1 wherein the plasticizing agent is sorbitol, glycerin, macrogols, or Andrisorb[™].
20. The soft elastic capsule of claim 19 wherein the plasticizing agent is present in initial state in the range of 4-18% by weight of the shell.
21. The soft elastic capsule of claim 1 wherein the ratio of the weight percentage of gelatin to plasticizing agent at said equilibrium state is in the range of 2:1 to 4:1.
22. The soft elastic capsule of claim 1 wherein the fill in an initial state comprises:
is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-

47
196

2-(2,6 dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane (lopinavir) in the range of 10- 35% by weight of the fill composition; polyethylene glycol in the range of 3-20% by weight of the fill composition; oleic acid in the range of 50-80% by weight of the fill; and wherein the shell in an initial state comprises:
gelatin in the range of 30-60% by weight of the shell, and
Andrisorb in the range of 4-18% by weight of the shell.

23. A method for making soft elastic capsules containing a pharmaceutical agent or a combination of pharmaceutical agents, the method comprising the steps of:
preparing a fill composition wherein the fill composition comprises
a pharmaceutical agent or combination of pharmaceutical agents,
a fill alcohol, and
a fatty acid;
preparing a shell composition wherein the shell composition comprises
gelatin, and
at least one plasticizing compound;
forming an soft elastic capsule wherein said shell has an initial state and an equilibrium state, wherein said initial state shell is underplasticized and said fill contains an alcohol amount in excess of an alcohol amount necessary to solubilize said pharmaceutical agent and said alcohol is not present in the initial state shell composition; and
equilibrating said soft elastic capsule wherein equilibrium state said shell becomes plasticized by the alcohol from said fill to provide suitable capsule hardness and said fill retains sufficient alcohol to maintain said pharmaceutical agent in solution.
24. The method of claim 23 wherein said pharmaceutical agent comprises a solubilized HIV inhibiting compound or a combination of solubilized HIV inhibiting compounds.
25. The method of claim 23 wherein said alcohol is propylene glycol or ethanol.

26. The method of claim 23 wherein said fatty acid is oleic acid.
27. The method of claim 23 wherein said fill further comprises a surfactant.
28. The method of claim 23 wherein the plasticizing agent is sorbitol, glycerin, macrogols, or Andrisorb™.

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
27 January 2005 (27.01.2005)

PCT

(10) International Publication Number
WO 2005/007070 A2

(51) International Patent Classification⁷: **A61K**
(21) International Application Number:
PCT/BR2004/000119
(22) International Filing Date: 19 July 2004 (19.07.2004)
(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
PI0302523-3 23 July 2003 (23.07.2003) BR

(71) Applicant (for all designated States except US):
CRISTÁLIA PRODUTOS QUÍMICOS FARMACÊUTICOS LTDA. [BR/BR]; 363 Paoletti Av., Itapira, SP, 13970-000 Itapira (BR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PACHECO, Ogari** [BR/BR]; 109 Dom Pedro I St., Nova Itapira, Itapira, SP, 13970-000 Itapira (BR). **RUSO, Elisa** [BR/BR]; 118 Dos Ipês St., Jardim Santa Marta, Itapira, SP, 13970-000 Itapira (BR). **RUSO, Valter** [BR/BR]; 118 Dos Ipês St., Jardim Santa Marta, Itapira, SP, 13970-000 Itapira (BR).

(74) Agent: **LLC INFO CONNECTION LTDA.**; 5555 Dom Hélder Câmara, RM 312, Pilares, 20771-001 Rio De Janeiro (BR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AP, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STABLE PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF HIV PROTEASE INHIBITORS AND PROCESS FOR PREPARING A CONCENTRATE PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF HIV PROTEASE INHIBITORS

(57) Abstract: The present invention describes a soluble and stable pharmaceutical composition for the administration of HIV protease inhibitors. More specifically, the composition comprises a solution of one or two HIV protease inhibitors in a combination of pharmaceutical acceptable organic solvents, a surfactant and a bioavailability enhancer. It is also described a process for preparing concentrate pharmaceutical compositions for the administration of HIV protease inhibitors. The composition of the present invention is suitable to prepare oral solutions for the administration of active drugs and to be encapsulated in hard gelatin capsules or soft gelatin capsules.

WO 2005/007070 A2

CLAIMS

1. A stable pharmaceutical composition characterized by comprising:
- 5 (a) [1S-[1R*, (R*), 3R*, 4R*]]-N-[4-[[(2,3-Dimethylphenoxy) acetyl]amino]- 3- hydroxy- 5-phenyl-1-(phenylmethyl) pentyl]tetrahydro-alfa-(1-methylethyl)-2-oxo-1-(2H)- pyrimidineacetamide (lopinavir), or its combination with [5S- (5R*, 8R*, 10R*, 11R*)] -10-hydroxy- 2-methyl -5- (1-methylethyl)-1- [2-(1-methylethyl) - 4 -
- 10 thiazolyl] - 3,6- dioxo - 8,11-bis (phenylmethyl) - acid 2,4,7,12 - tetraazatridecan - 13-oic 5-thiazolilmethyl ester (ritonavir);
- (b) A mixture between an alcoholic solvent and an alcoholic co-solvent;
- 15 (c) A mixture of medium chain mono/diglycerides of C₈₋₁₀;
- (d) A pharmaceutical acceptable surfactant;
- (e) An antioxidant;
- (f) Optionally, an emulsion stabilizer;
- (g) Optionally, a polarity corrector.
- 20 2. A pharmaceutical composition of claim 1, wherein [1S-[1R*, (R*), 3R*, 4R*]] -N- [4- [[(2,3-Dimethylphenoxy) acetyl]amino]- 3- hydroxy- 5-phenyl-1-(phenylmethyl) pentyl]tetrahydro-alfa-(1-methylethyl)-2-oxo-1-(2H)- pyrimidineacetamide (lopinavir) is used in a
- 25 concentration from 1.0% to 60% in weight of the final composition, more preferably in a concentration from 10% to 50% in weight of the final composition;
3. A pharmaceutical composition of claim 1, characterized by comprising a combination between [1S-[1R*, (R*), 3R*, 4R*]]-N- [4- [[(2,3-Dimethylphenoxy) acetyl]amino]- 3-
- 30 hydroxy- 5-phenyl-1-(phenylmethyl) pentyl]tetrahydro-

53
185
200

5 alfa-(1-methylethyl)-2-oxo-1-(2H)-pyrimidineacetamide
 (lopinavir) and [5S- (5R*,8R*,10R*,11R*)] -10-hydroxy- 2-
 methyl -5- (1-methylethyl)-1- [2-(1-methylethyl) - 4 -
 tiazolyl] - 3,6- dioxo - 8,11-bis (phenylmethyl) - acid
10 2,4,7,12 - tetraazatridecan - 13-oic 5-thiazolilmethyl
 ester (ritonavir), which are present in a weight ratio
 ranging from 9:1 to 1:9 respectively, being the
 combination used in a concentration ranging from 1.0% to
 60% in weight of the final composition, more preferably
15 in a concentration ranging from 10% to 50% in weight of
 the final composition;

4. A pharmaceutical composition according to claim 1,
 characterized by the alcoholic solvent is used in a
 concentration from 5.0% to 20% in weight of the final
15 composition, more preferably in a concentration from 5.0%
 to 15% in weight of the final composition;

5. A pharmaceutical composition according to claim 1,
 characterized by the alcoholic co-solvent is used in a
 concentration from 5.0% to 20% in weight of the final
20 composition, more preferably in a concentration from 5.0%
 to 15% in weight of the final composition;

6. A pharmaceutical composition according to claim 1,
 characterized by the alcoholic solvent and co-solvent are
 used in a concentration from 10% to 40% in weight of the
25 final composition, more preferably used in a
 concentration from 10% to 30% in weight of the final
 composition;

7. A pharmaceutical composition according to claim 1,
 characterized by the mixture of medium chain
30 mono/diglycerides of C₈₋₁₀ is used in a concentration from
 20% to 80% in weight of the final composition, more
 preferably in a concentration from 20% to 70% in weight
 of the final composition;

109
201

8. A pharmaceutical composition according to claim 1, characterized by the surfactant is used in a concentration from 0.1% to 20%;
- 5 9. A pharmaceutical composition according to claim 1, characterized by the antioxidant is used in a concentration from 0.001% to 2.0% in weight of the final composition;
- 10 10. A pharmaceutical composition according to claim 1, characterized by the alcoholic solvent is ethanol and the alcoholic co-solvent is propylene glycol;
11. A pharmaceutical composition according to claim 1, characterized by the surfactant is polyethoxylated castor oil 35, and/or polyethoxylated hydrogenated castor oil 40, and or polysorbates 20, 40, 60 or 80;
- 15 12. A pharmaceutical composition according to claim 1, characterized by the antioxidant is the butylated hydroxytoluene and/or alpha-tocopherol;
13. A pharmaceutical composition according to claim 1, characterized by using an emulsion stabilizing agent in a concentration from 0% to 60% in weight of the final composition;
- 20 14. A pharmaceutical composition according to claim 1, characterized by the emulsion stabilizing agent is the polyethyleneglycol 400 (PEG 400);
- 25 15. A pharmaceutical composition according to claim 1, characterized by using a polarity corrector agent in a concentration from 0% to 0.5% in weight of the final composition;
- 30 16. A pharmaceutical composition according to claim 1, characterized by the polarity corrector agent used is citric acid and/or ascorbic acid;

55
182
202

17. A pharmaceutical composition according to claims 1 to 16, characterized by being used for oral administration as a solution, hard gelatin capsules and/or soft gelatin capsules;
- 5 18. A pharmaceutical composition according to claims 1 to 16, characterized by being preferably used for oral administration as soft gelatin capsules;
19. A pharmaceutical composition according to claim 1 to 16, characterized by being used in the treatment of viral infections;
- 10 20. A pharmaceutical composition according to claims 1 to 16, characterized by being used in medicine or veterinary.
21. A process for preparing pharmaceutical compositions of [1S-[1R*,(R*),3R*,4R*]] - N- [4-[[(2,3-Dimethylphenoxy) acetyl]amino]- 3- hydroxy- 5-phenyl-1-(phenylmethyl) 15 pentyl]tetrahydro -alfa- (1-methylethyl)-2-oxo-1-(2H)-pyrimidineacetamide (lopinavir), or its combination with [5S- (5R*,8R*,10R*,11R*)] -10-hydroxy- 2-methyl -5- (1-methylethyl)-1- [2-(1-methylethyl) - 4 - thiazolyl] - 3,6-dioxo - 8,11-bis (phenylmethyl) - acid 2,4,7,12 - 20 tetraazatridecane - 13-oic 5-thiazolylmethyl ester (ritonavir), characterized by comprising the following steps:
- 25 (a2) Completely dissolving lopinavir or its combination with ritonavir in a sufficient amount of the alcoholic solvent of C₂₋₄, under controlled temperature;
- (b2) Eliminating solid particles by filtration;
- 30 (c2) Adding a mixture of mono/diglycerides, the antioxidant, the emulsion stabilizer and the polarity corrector in the appropriate amount for using in the composition;