ALUVIA™
Lopinavir/ritonavir tablets

PRODUCT NAME

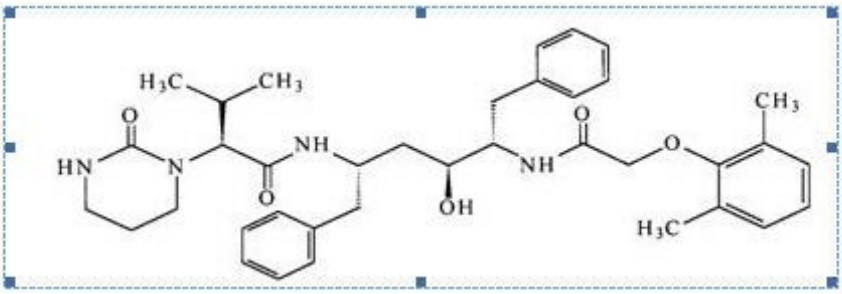
Lopinavir/ritonavir

Trade Names
Aluvia™

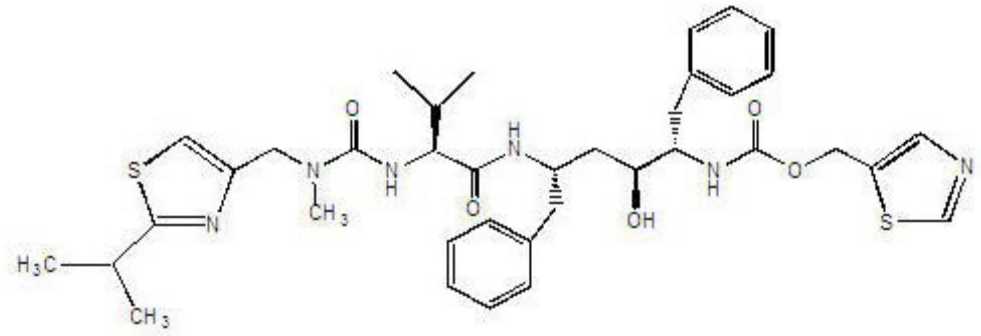
DESCRIPTION

Lopinavir/ritonavir is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. As co-formulated in Aluvia, ritonavir inhibits the cytochrome P450 3A (CYP3A)-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water. Lopinavir is chemically designated as [1S-[1R*, (R*), 3R*, 4R*]]-N-[4-[[2,6- dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro- alpha-(*1*-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir has the following structural formula:



Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Lopinavir/ritonavir film coated tablets are available for oral administration in a strength of 200 mg of lopinavir and 50 mg of ritonavir or 100 mg of lopinavir and 25 mg of ritonavir with the following inactive ingredients: copovidone sorbitan laurate, colloidal anhydrous silica, and sodium stearyl fumarate.

The following are the ingredients in the film coating:

200/50 mg Tablets:

Strength and Color of Tablet	List of ingredients in the film coating
200/50 mg Red tablet	Hypromellose, titanium dioxide, macrogols type 400, hydroxypropyl cellulose, talc, colloidal anhydrous silica, macrogols type 3350, red ferric oxide E172, and polysorbate 80

100/25 mg Tablets:

Strength and Color of Tablet	List of ingredients in the film coating
100/25 mg Pale pink tablet	Polyvinyl alcohol, titanium dioxide, talc, macrogols type 3350 (Polyethylene glycol 3350), red ferric oxide E172

INDICATIONS

Lopinavir/ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-infection as a second line treatment. This indication is based on analyses of plasma HIV RNA levels and CD_4 cell counts in a controlled study of lopinavir/ritonavir of 48 weeks duration, and in smaller uncontrolled dose-ranging studies of lopinavir/ritonavir of 144-360 weeks duration. At present, there are no results from controlled trials evaluating the effect of lopinavir/ritonavir on clinical progression of HIV.

Once daily administration of lopinavir/ritonavir has not been studied in therapy-experienced patients.

DOSAGE AND ADMINISTRATION

Adults

Lopinavir/ritonavir tablets should be swallowed whole and not be chewed, broken or crushed.

The recommended oral dose of lopinavir/ritonavir is as follows:

Therapy-Naïve Patients

* Lopinavir/ritonavir tablets 400/100 mg (given as two, 200/50 mg tablets) twice-daily with or without food.
* Lopinavir/ritonavir tablets 800/200 mg (given as four, 200/50 mg tablets) once daily taken with or without food.

Therapy-experienced patients

* Lopinavir/ritonavir tablets 400/100 mg (given as two, 200/50 mg tablets) twice-daily taken with or without food.

Once daily administration of lopinavir/ritonavir has not been studied in therapy-experienced patients.

Concomitant Therapy

Omeprazole and Ranitidine

Lopinavir/ritonavir tablets can be used in combination with acid reducing agents (omeprazole and ranitidine) with no dose adjustment (see **Table 1).**

Efavirenz, Nevirapine, Amprenavir, or Nelfinavir

Lopinavir/ritonavir 400/100 mg tablets can be used twice daily in combination with these drugs with no dose adjustment (see PRECAUTIONS Drug Interactions).

Lopinavir/ritonavir should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

Concomitant therapy: Efavirenz, nevirapine, amprenavir or nelfinavir
A dose increase of lopinavir/ritonavir to 533/133 mg twice-daily taken with food is recommended when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

Dosing During Pregnancy and the Postpartum Period

Tablets

- No dose adjustment is required for lopinavir/ritonavir during pregnancy and postpartum.
- Once daily administration of lopinavir/ritonavir is not recommended for pregnant women.

Pediatric Patients Lopinavir/ritonavir should not be administered once daily in pediatric patients. The adult dose of lopinavir/ritonavir tablets (400/100 mg BID) without concomitant efavirens, nevirapine, nelfinavir of amprenavir may be used in children weighing 35 kg or greater or with a Body Surface Area (BSA) of 1.4 m^2 or

greater. For children weighing less than 35 kg or with a BSA between 0.6 to 1.4 m^2 and able to swallow tablets, please refer to the dosing tables below.
The following table contains dosing guidelines for lopinavir/ritonavir 100/25 mg tablets based on BSA:

Pediatric Dosing Guidelines Based on BSA Without Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Body Surface Area * (m^2)	**Recommended Number of 100/25 mg Tablets Twice-Daily**
≥ 0.6 to < 0.9	2 tablets (200/50 mg)
> 0.9 to < 1.4	3 tablets (300/75 mg)
≥ 1.4	4 tablets (400/100 mg)

Body surface area can be calculated with the following equation:

$$BSA\ (m^2) = \sqrt{\frac{Ht\ (Cm) \times Wt\ (kg)}{3600}}$$

Concomitant Therapy: Efavirenz, Nevirapine, Nelfinavir, or Amprenavir

The following table contains dosing guidelines for lopinavir/ritonavir 100/25 mg tablets based on BSA when used in combination with efavirenz, nevirapine, nelfinavir or amprenavir in children:

Pediatric Dosing Guidelines Based on BSA With Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Body Surface Area* (m^2)	**Recommended number of 100/25 mg Tablets twice-Daily**
≥0.6 to < 0.8	2 tablets (200/50 mg)
≥0.8 to <1.2	3 tables (300/75 mg)
≥ 1.2 to <1.7	4 tablets (400/100 mg)
≥ 1.7	5 tablets (500/125 mg)

The following table contains dosing guidelines for lopinavir/ritonavir 100/25 mg tablets based on body weight:

Pediatric Dosing Guidelines Based on Weight Without Cocomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Weight (kg)	**Number of 100/25 mg Tablets twice-daily**
15 to 25 kg	2
> 25 to 35 kg	3
≥ 35 kg	4#

Alternatively, two 200/50 mg tablet may be used for this dose in patients who can swallow the larger tablet.

Concomitant Therapy; Efavirenz, nevirapine, nelfinavir or amprenavir

The following table contains dosing guidelines for lopinavir/ritonavir 100/25 mg tablets based on body weight when used in combination with efavirenz, nevirapine, nelfinavir or amprenavir in children:

Pediatric Dosing Guidelines Based on Weight with Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Weight (kg)	Number of 100/25 mg tablets twice-daily
15 to 20 kg	2
> 20 to 30 kg	3
> 30 kg to 45 kg	4#
> 45 kg	5
# Alternatively, two 200/50 mg tablet may be used for this dose in those patients who can swallow the larger tablet.	

CONTRAINDICATIONS

Lopinavir/ritonavir is contraindicated in patients with known hypersensitivity to lopinavir, ritonavir, or any excipients.

Lopinavir/ritonavir should not be co-administered concurrently with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in **Table 1**.

Table 1	
Drugs which should not be co-administered with Lopinavir/ritonavir	
Drug Class	**Drug within Class Not to be Co-administered**
Alpha1-adrenoreceptor antagonist	Alfuzosin HCl
Antianginal	Ranolazine
Antiarrithmic	Dronadrone
Antibiotics	Fusidic acid
Anticancer Agents	Apalutamide, Neratinib
Antigout	Colcihine in patient with renal and/or hepatic impairement
Antihistamines	Astemizole, terfenadine
Antipsychotic	Blonanserin , Lurasidone, Pimozide
Benzodiazepines	Midazolam, triazolam

Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine
GI motility agent	Cisapride
Herbal product	St. John's Wort (*Hypericum perforatum*)
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin
Microsomal triglyceride transfer protein (MTTP) Inhibitor	Lomitapide
Long acting beta-adrenoceptor agonist	Salmeterol
Neuroleptics	Pimozide
PDE5 enzyme inhibitor	Sildenafil* (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH)
* see WARNINGS AND PRECAUTIONS and DRUGS INTERACTIONS for co-administration of sildenafil in patients with erectile dysfunction	

Patient with severe hepatic insufficiency

WARNINGS AND PRECAUTIONS

Drug Interactions

Lopinavir/ritonavir is an inhibitor of the P450 isoform CYP3A. Co-administration of lopinavir/ritonavir and drugs primarily metabolized by CYP3A or may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS-Table 1, DRUG INTERACTIONS, and *Pharmacokinetic Properties: Drug-Drug Interactions*).**

Antigout agents Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see **CONTRAINDICATIONS** and **DRUG).**

Anti-mycobacterial

Standard dose lopinavir/ritonavir should not be co-administered with rifampin because large decreases in lopinavir concentrations may significantly decrease the therapeutic effect (see **DRUG INTERACTIONS**).

Antipsychotics
Caution should be exercised when lopinavir/ritonavir is co-administered with quetiapine. Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities (see **DRUG INTERACTION**).

Corticosteroids

Concomitant use of lopinavir/ritonavir and fluticasone, or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

Concomitant use of lopinavir/ritonavir and fluticasone propionate can significantly increase fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when lopinavir/ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide (see **DRUG INTERACTIONS**).

PDE5 inhibitors

Co-administration of lopinavir/ritonavir with avanafil is not recommended. Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving lopinavir/ritonavir. Co-administration of lopinavir/ritonavir with these drugs is expected to substantially increase their concentrations and may result in increased associated adverse events such as hypotension, and prolonged erection. Concomitant use of sildenafil with lopinavir/ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Herbal Products

Patients on lopinavir/ritonavir should not use products containing St. John's Wort *(Hypericum perforatum)* because co-administration may be expected to reduce plasma concentrations of protease inhibitors. This may result in loss of therapeutic effect and development of resistance to lopinavir or to the therapeutic class of protease inhibitors (see **CONTRAINDICATIONS and DRUG INTERACTIONS**).

HMG-CoA Reductase Inhibitors

Concomitant use of lopinavir/ritonavir with lovastatin or simvastatin is contraindicated (see **CONTRAINDICATIONS**).

Caution should be exercised if HIV protease inhibitors, including lopinavir/ritonavir, are used concurrently with rosuvastatin or with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (e.g., atorvastatin), as this may increase the potential for serious reactions such as myopathy, including rhabdomyolysis (see **DRUG INTERACTIONS**).

Tipranavir

In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, tipranavir (500 mg twice daily) with ritonavir (200 mg twice daily), co-administered with lopinavir/ritonavir (400/100 mg twice daily), resulted in a 55% and 70% reduction in lopinavir AUC and Cmin respectively. The concomitant administration of lopinavir/ritonavir and tipranavir with low dose ritonavir is therefore not recommended.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease

inhibitor therapy and these events has not been established. Consideration should be given to the monitoring of blood glucose.

Pancreatitis

Pancreatitis has been observed in patients receiving lopinavir/ritonavir therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to lopinavir/ritonavir has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **WARNINGS AND PRECAUTIONS: Lipid Elevations**). Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during lopinavir/ritonavir therapy.

Hepatic Impairment

Lopinavir/ritonavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function. Lopinavir/ritonavir has not been studied in patients with severe hepatic impairment. Pharmacokinetic data suggests increases in lopinavir plasma concentrations of approximately 30% as well as decreases in plasma protein binding in HIV and HCV co-infected patients with mild to moderate hepatic impairment (see **PHARMACOLOGIC PROPERTIES: Pharmacokinetic Properties**). Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with lopinavir/ritonavir therapy has not been established.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as early as 7 days after the initiation of lopinavir/ritonavir in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with lopinavir/ritonavir therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of lopinavir/ritonavir treatment.

Resistance/Cross-Resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of lopinavir/ritonavir therapy on the efficacy of subsequently administered protease inhibitors is under investigation (see **PHARMACOLOGIC PROPERTIES: *Microbiology*).**

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. Neither a causal relationship or a mechanism of action between protease inhibitor therapy and these events has been established.

PR Interval Prolongation

Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Rare reports of second or third degree atrioventricular block in patients with underlying structural heart disease and preexisting conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. Lopinavir/ritonavir should be used with caution in such patients (see **PHARMACOLOGIC PROPERTIES: Effects on Electrocardiogram**).

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations

Treatment with lopinavir/ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS: Tables 2 - 4**). Triglyceride and cholesterol testing should be performed prior to initiating lopinavir/ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **WARNINGS AND PRECAUTIONS: *HMG-CoA Reductase Inhibitors*** for additional information on potential drug interactions with lopinavir/ritonavir and HMG CoA reductase inhibitors.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including lopinavir/ritonavir. During the initial phase of combination antiretroviral treatment when the immune system responds, patients may develop an inflammatory response to asymptomatic or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci pneumonia*, or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Osteonecrosis

Although the etiology is considered to multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, high body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if experience joint aches and pain, joint stiffness or difficulty in movement.

Geriatric Use

Clinical studies of lopinavir/ritonavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate

caution should be exercised in the administration and monitoring of lopinavir/ritonavir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use

The safety and pharmacokinetic profiles of lopinavir/ritonavir in pediatric patients below the age of six months have not been established. In HIV-infected patients age six months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of lopinavir/ritonavir in pediatric patients in clinical trials is ongoing (see **DESCRIPTION OF CLINICAL STUDIES**). Lopinavir/ritonavir once daily has not been evaluated in pediatric patients.

DRUG INTERACTIONS

Lopinavir/ritonavir is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of lopinavir/ritonavir and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **WARNINGS AND PRECAUTIONS**). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when co-administered with lopinavir/ritonavir. Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in **Table 1** under **CONTRAINDICATIONS**.

Anti-HIV Agents

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Stavudine and Lamivudine

No change in the pharmacokinetics of lopinavir was observed when lopinavir/ritonavir was given alone or in combination with stavudine and lamivudine.

Didanosine

It is recommended that didanosine be administered on an empty stomach; therefore, didanosine may be co-administered with lopinavir/ritonavir tablets without food.

Zidovudine and Abacavir

Lopinavir/ritonavir induces glucuronidation, therefore lopinavir/ritonavir has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Tenofovir

A study has shown lopinavir/ritonavir increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and tenofovir should be monitored for tenofovir-associated adverse events.

All

Increased CPK, myalgia, myositis, and rarely, rhabdomyolysis have been reported with PIs, particularly in combination with NRTIs.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine

No change in the pharmacokinetics of lopinavir was apparent in healthy adult subjects during nevirapine and lopinavir/ritonavir co-administration. Results from a study in HIV-positive pediatric subjects revealed a decrease in lopinavir concentrations during nevirapine co-administration (see **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**). The effect of nevirapine in HIV-positive adults is expected to be similar to that in pediatric subjects and lopinavir concentrations may be decreased. The clinical significance of the pharmacokinetic interaction is unknown.

For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase of lopinavir/ritonavir capsules and oral solution to 533/133 mg BID , or lopinavir/ritonavir tablets to 500/125 mg BID should be considered when co-administered with nevirapine. Lopinavir/ritonavir should not be administered once daily in combination with nevirapine.

Efavirenz

When used in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in multiple protease inhibitor-experienced subjects, increasing the dose of lopinavir/ritonavir 33.3% from 400/100 mg (three (3) soft gel capsules) BID to 533/133 mg (four (4) soft gel capsules) BID, or 25% from 400/100 mg (two (2) 200/50 mg tablets) BID to 500/125 mg (two (2) 200/50 tablets + one (1) 100/25 mg tablet). yielded similar lopinavir plasma concentrations as compared to historical data of lopinavir/ritonavir 400/100 mg BID.

For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase of lopinavir/ritonavir capsules and oral solution to 533/133 mg BID, or lopinavir/ritonavir tablet to 500/125 mg BID should be considered when co-administered with efavirenz.

Increasing the dose of lopinavir/ritonavir tablets to 600/150 (three (3) tablets) BID co-administered with efavirenz significantly increased the lopinavir plasma concentrations approximately 36% and ritonavir concentrations approximately 56% to 92% compared to lopinavir/ritonavir tablets 400/100 mg BID without efavirenz (see **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**).

NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with lopinavir/ritonavir. Lopinavir/ritonavir should not be administered once daily in combination with efavirenz.

Delavirdine

Delavirdine has the potential to increase plasma concentrations of lopinavir.

Rilpivirine
Concomitant use of lopinavir/ritonavir with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required. Refer to the rilpivirine prescribing information.

Etravirine
Concomitant use of lopinavir/ritonavir with etravirine causes a decrease in the plasma concentrations of etravirine, but no dose adjustment is required. Refer to the etravirine prescribing information.

Protease Inhibitors (PIs)

Amprenavir

Lopinavir/ritonavir is expected to increase concentrations of amprenavir (amprenavir 750 mg BID plus lopinavir/ritonavir produces increased AUC, similar C_{max}, increased C_{min}, relative to amprenavir 1200 mg BID). Co-administration of lopinavir/ritonavir and amprenavir result in decreased concentrations of lopinavir. The dose of lopinavir/ritonavir may need to be increased during co-administration of amprenavir, particularly in patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir (see **DOSAGE AND ADMINISTRATION** and **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**). Lopinavir/ritonavir should not be administered once daily in combination with amprenavir.

Fosamprenavir
A study has shown that co-administration of lopinavir/ritonavir with fosamprenavir lowers amprenavir and lopinavir concentrations. Appropriate doses of the combination of fosamprenavir and lopinavir/ritonavir with respect to safety and efficacy have not been established

Indinavir

Lopinavir/ritonavir is expected to increase concentrations of indinavir (indinavir 600 mg BID plus lopinavir/ritonavir produces similar AUC, decreased Cmax, increased Cmin relative to indinavir 800 mg TID. The dose of indinavir may need to be decreased during co-administration with lopinavir/ritonavir 400/100 mg BID (see **PHARMACOLOGIC PROPERTIES**: **Table 9**). Lopinavir/ritonavir once daily has not been studied in combination with indinavir.

Nelfinavir

Lopinavir/ritonavir is expected to increase concentrations of nelfinavir and increased M8 metabolite of nelfinavir (nelfinavir 1000 mg BID plus lopinavir/ritonavir produces similar AUC, similar C_{max}, increased C_{min} relative to nelfinavir 1250 mg BID). Co-administration of lopinavir/ritonavir and nelfinavir result in decreased concentrations of lopinavir. Lopinavir/ritonavir should not be administered once daily in combination with nelfinavir.

Ritonavir

When lopinavir/ritonavir was co-administered with an additional 100 mg ritonavir twice daily, lopinavir AUC increased 33% and C_{min} increased 64% as compared to lopinavir/ritonavir 400/100

mg (three (3) soft gel capsules) twice daily (see **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**).

Saquinavir

Lopinavir/ritonavir is expected to increase concentrations of saquinavir (saquinavir 800 mg BID plus lopinavir/ritonavir produces increased AUC, increased C_{max}, increased C_{min} relative to saquinavir 1200 mg TID). The dose of saquinavir may need to be decreased when co-administered with lopinavir/ritonavir 400/100 mg BID (see **PHARMACOLOGIC PROPERTIES**: **Table 9**). Lopinavir/ritonavir once daily has not been studied in combination with saquinavir.

HCV- Protease Inhibitors

Simeprevir

Concomitant use of lopinavir/ritonavir and simeprevir may result in increased plasma concentrations of simeprevir. It is not recommended to co-administer lopinavir/ritonavir and simeprevir

Telaprevir

Concomitant administration of telaprevir and lopinavir/ritonavir resulted in reduced telaprevir steady-state exposure, while the lopinavir steady-state exposure was not affected (see **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**).

Boceprevir

Concomitant administration of boceprevir and lopinavir/ritonavir resulted in reduced boceprevir and lopinavir steady-state exposure (see **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**). It is not recommended to co-administer lopinavir/ritonavir and boceprevir.

Glecaprevir/pibrentasvir:
Concomitant administration of glecaprevir/pibrentasvir and lopinavir/ritonavir is not recommended due to an increased risk of ALT elevations associated with increased GLE exposure

Sofosbuvir/velpatasvir/voxilaprevir:
Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and lopinavir/ritonavir is not recommended due to the potential for increased toxicity, which may negatively impact compliance.

Ombitasvir/paritaprevir/ritonavir and dasabuvir*:*

Concentrations of ombitasvir, paritaprevir, and ritonavir may be increased when co-administered with lopinavir/ritonavir, therefore, co-administration is not recommended.

HIV CCR5 – antagonist

Maraviroc

Concurrent administration of maraviroc with lopinavir/ritonavir will increase plasma levels of maraviroc (see **PHARMACOLOGIC PROPERTIES**: **Table 9**). The dose of maraviroc should be decreased during co-administration with lopinavir/ritonavir 400/100 mg BID. For further details, see complete prescribing information for maraviroc.

Other Drugs

Analgesic

Fentanyl: Lopinavir/ritonavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with lopinavir/ritonavir.

Antiarrhythmics (amiodarone, bepridil, (see **CONTRAINDICATIONS**), systemic lidocaine and quinidine): Concentrations may be increased when co-administered with lopinavir/ritonavir.
Caution is warranted and therapeutic concentration monitoring is recommended when available.

Digoxin: A literature report has shown that co-administration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when co-administering lopinavir/ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.

Anticancer Agents (e.g. abemaciclib, apalutamide, dasatinib, ibrutinib, encorafenib, ivosidenib, neratinib, nilotinib, venotoclax, vincristine, vinblastine): May have their serum concentrations increased when co-administered with lopinavir/ritonavir resulting in the potential for increased adverse events, some of which may be serious.
Coadministration of venetoclax or ibrutinib with lopinavir/ritonavir could increase venetoclax or ibrutinib exposure potentially resulting in a serious risk of tumor lysis syndrome. Coadministration of encorafenib or ivosidenib with lopinavir/ritonavir could increase encorafenib or ivosidenib exposure potentially increasing the risk of serious adverse events such as QT interval prolongation.

For venotoclax, ibrutinib, encorafenib, ivosidenib nilotinib and dasatinib, refer to their prescribing information for dosing instructions.

Coadministration of apalutamide is contraindicated with Aluvia since apalutamide may decrease exposure of luviah potential loss of virologic response. In addition, co-administration of apalutamide and Aluvia may lead to increased exposure of apalutamide resulting in increased potential for adverse events including seizure.

Anticoagulants

Warfarin concentrations may be affected when co-administered with lopinavir/ritonavir. It is recommended that INR (international normalized ratio) be monitored.

Rivaroxaban: Co-adminstration of rivaroxaban and lopinavir/ritonavir may increase rivaroxaban exposure which may increase the risk of bleeding.

Anticonvulsants

(Phenobarbital, phenytoin, carbamazepine): These drugs are known to induced CYP3A4 and may decrease lopinavir concentrations. Lopinavir/ritonavir should not be administered once daily in combination with phenobarbital, phenytoin, or carbamazepine.

In addition, co-administration of phenytoin and lopinavir/ritonavir resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with lopinavir/ritonavir.

Lamotrigine and valproate: Co-administration of lopinavir/ritonavir and either of these drugs was associated with reduction in exposure of the anticonvulsant; 50% reduction in lamotrigine exposure has been reported. Use with caution. A dose increase of the anticonvulsant may be needed when co-administered with lopinavir/ritonavir and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments (see **PHARMACOLOGIC PROPERTIES**: **Table 9)**.

Antidepressants

Bupropion: Concurrent administration of bupropion with lopinavir/ritonavir will decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion).

Trazodone: Concomitant use of ritonavir and trazodone may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor such as lopinavir/ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Antifungals

Ketoconazole and itraconazole may have serum concentrations increased by lopinavir/ritonavir (see **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**). High doses of ketoconazole and itraconazole (greater than 200 mg/day) are not recommended.

Voriconazole: A study has shown that co-administration of ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of lopinavir/ritonavir and voriconazole should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Antigout Agents

Concentrations of colchicine are expected to increase when co-administered with lopinavir/ritonavir. Refer to the colchicine label for prescribing information.

Life –threatening and fatal drug interaction have been reported in patients treated with colchicine and ritonavir (see Contraindication and Warning and precautions).

Anti-infective

Moderate increases in clarithromycin AUC are expected when co-administered with lopinavir/ritonavir. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered.

Anti-mycobacterial

When rifabutin and lopinavir/ritonavir were co-administered for ten days, rifabutin (parent drug and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3.5- and 5.7-fold, respectively (see **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**). On the basis of these data, a rifabutin dose reduction of 75% (i.e. 150 mg every other day or three times per week) is recommended when administered with lopinavir/ritonavir. Further dose reduction of rifabutin may be necessary.

Due to large decreases in lopinavir concentrations, rifampin should not be used in combination with standard dose lopinavir/ritonavir (see **WARNINGS AND PRECAUTIONS: *Drug Interactions***). The use of Rifampin with standard dose lopinavir/ritonavir, may lead to loss of virologic response and possible resistance to lopinavir/ritonavir or to the class of protease inhibitors or other co-administered antiretroviral agents. Co-administration of rifampicin with 800/200 mg lopinavir/ritonavir BID resulted in decreases in lopinavir of up to 57% and with lopinavir/ritonavir 400/400 mg BID resulted in decreases of up to 7% when compared to lopinavir/ritonavir 400/100 mg BID dosed in the absence of rifampicin (see **PHARMACOLOGIC PROPERTIES: Tables 8 and 9**). ALT and AST elevations have been noted in studies with higher doses of lopinavir/ritonavir co-administered with rifampicin and may be dependent on the sequence of dose administration. If co-administration is being considered, lopinavir/ritonavir should be initiated at standard doses for approximately 10 days prior to addition of rifampicin. Lopinavir/ritonavir dose should then be titrated upward. Close monitoring of liver function is indicated.

Bedaquiline: In a healthy volunteer drug interaction study of 400 mg single dose bedaquiline and lopinavir/ritonavir 400/100 mg twice daily for 24 days, bedaquiline exposures (AUC) were increased by 22%. Therefore, combination of Bedaquiline with lopinavir/ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of belaquiline with lopinavir/ritonavir must be done with cautious. More frequent electrocardiogram monitoring & monitoring of transaminase is recommended.

Antiparasitic

Decreases in the therapeutic concentration of atovaquone are possible when co-administered with lopinavir/ritonavir. Increases in atovaquone doses may be necessary.

Corticosteroids
Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations

Inhaled, injectable or intranasal, Fluticasone propionate, budesonide, triamcinolone.: Concomitant use of lopinavir/ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Consider alternatives to fluticasone propionate, particularly for long-term use (see **WARNINGS AND PRECAUTIONS: *Drug Interactions***).

Dihydropyridines Calcium Channel Blockers

(e.g. felodipine, nifedipine, nicardipine): May have their serum concentrations increased by lopinavir/ritonavir.

PDE5 inhibitors

Avanafil: Co-administration of lopinavir/ritonavir with avanafil is expected to result in large increases in avanafil exposure and is contraindicated (see **WARNINGS AND PRECAUTIONS: Drug Interactions).**

Sildenafil: Use sildenafil for the treatment of erectile dysfunction with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events (see **WARNINGS AND PRECAUTIONS: *Drug Interactions***).

Concomitant use of sildenafil with lopinavir/ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients (see **CONTRAINDICATIONS**).

Tadalafil: Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events (see **WARNINGS AND PRECAUTIONS: *Drug Interactions*).**

When tadalafil is administered in patients with pulmonary arterial hypertension who are receiving lopinavir/ritonavir, refer to the tadalafil label for prescribing information.

Vardenafil: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events (see **WARNINGS AND PRECAUTIONS: *Drug Interactions*).**

Elagolix: Coadministration of elagolix with lopinavir/ritonavir could increase elagolix exposure through inhibition of OATP, CYP 3A, and P-gp. Known serious adverse events for elagolix include suicidal ideation and hepatic transaminase elevations. In addition, elagolix is a weak/moderate inducer of CYP3A, which may decrease exposure of lopinavir/ritonavir. Refer to the elagolix label for dosing information with strong CYP-3A4 inhibitors.

Kinase Inhibitors (also see anticancer agents above)
Fostamatinib: Coadministration of fostamatinib with lopinavir/ritonavir could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia.

Herbal Products

Patients on lopinavir/ritonavir should not use products containing St John's Wort concomitantly, since this combination may be expected to result in reduced plasma concentrations of lopinavir/ritonavir. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS: *Drug Interactions*).**

HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with lopinavir/ritonavir. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these drugs with lopinavir/ritonavir is contraindicated (see **CONTRAINDICATIONS**).

Atorvastatin is less dependent on CYP3A for metabolism. When atorvastatin was given concurrently with lopinavir/ritonavir, a mean 4.7-fold and 5.9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with lopinavir/ritonavir, the lowest possible doses of atorvastatin should be administered. Results from a drug interaction study with lopinavir/ritonavir and pravastatin reveal no clinically significant interaction (see **PHARMACOLOGIC PROPERTIES**: **Tables 8 and 9**). The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with lopinavir/ritonavir. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see **WARNINGS AND PRECAUTIONS: *Drug Interactions***).

Lomitapide

Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated.

Immunosuppressants

Concentrations of these drugs (e.g. cyclosporine, tacrolimus and sirolimus (rapamycin)) may be increased when co-administered with lopinavir/ritonavir. More frequent therapeutic concentration monitoring is recommended until blood levels of these products have stabilized.

Methadone

Lopinavir/ritonavir was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended (see **PHARMACOLOGIC PROPERTIES**: **Table 9**).

Oral Contraceptives or Patch Contraceptives

Since levels of ethinyl estradiol may be decreased, alternative or additional contraceptive measures are to be used when estrogen-based oral contraceptives or patch contraceptives and lopinavir/ritonavir are co-administered (see **PHARMACOLOGIC PROPERTIES**: **Table 9**).

Vasodilating agents

Co-administration of bosentan and lopinavir/ritonavir increased steady-state bosentan maximum concentrations (C_{max}) and area-under-the-curve (AUC) by 6-fold and 5-fold, respectively. Refer to the bosentan label for prescribing information.

Clinically Significant Drug Interactions Are Not Expected

Drug interaction studies reveal no clinically significant interaction with desipramine (CYP2D6 probe), omeprazole or ranitidine (see **PHARMACOLOGIC PROPERTIES**: **Tables 8 and 9**).

Clinical studies showed no clinically significant interaction between lopinavir/ritonavir and raltegravir.

Based on known metabolic profiles, clinically significant drug interactions are not expected between lopinavir/ritonavir and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, or fluconazole in patients with normal renal and hepatic function.

PREGNANCY AND LACTATION

Pregnancy

As a general rule, when deciding to use antiretroviral agents for treatment of HIV in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterize the safety for the foetus.
There are no adequate and well controlled studies of Aluvia in pregnant women. In post marketing surveillance through the Antiretroviral Pregnancy Registry, established since January 1989. An increased risk of birth defects exposures with Aluvia has not been reported among over 600 women exposed during the first trimester.
The prevalence of birth defects after any trimester exposures to lopinavir is comparable to the prevalence observed in the general population. No pattern of birth defects suggestive of a common etiology was seen. Studies in animal data have shown reproductive toxicity. Based on the limited data mentioned, the malformative risk is unlikely in human.

Lactation

Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. As a general rule, it is recommended that mothers infected by HIV do not breast-feed their babies under any circumstances, in order to avoid transmission of HIV.

Fertility

Animal studies have shown no effects on fertility. No Human data on the effect of lopinavir/ritonavir on fertility are available.

ADVERSE REACTIONS

Adults

Treatment-Emergent Adverse Reactions

The safety of lopinavir/ritonavir has been investigated in over 2,600 patients in Phase II-IV clinical trials, of which more than 700 have received a dose of 800/200 mg (6 capsules or 4 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies, lopinavir/ritonavir was used in combination with efavirenz or nevirapine.

Commonly reported adverse reactions to lopinavir/ritonavir included diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. Diarrhea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridemia and hypercholesterolemia may occur later. The following have been identified as adverse reactions of moderate or severe intensity (**Table 2**):

Table 2 Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult		
System Organ Class (SOC) and Adverse Reaction	**n**	**%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia*	54	2.067
Leukopenia and neutropenia*	44	1.685
Lymphadenopathy*	35	1.340
CARDIAC DISORDERS		
Atherosclerosis such as myocardial infarction*	10	0.383
Atrioventricular block*	3	0.115
Tricuspid valve incompetence*	3	0.115
EAR AND LABYRINTH DISORDERS		
Vertigo*	7	0.268
Tinnitus	6	0.230
ENDOCRINE DISORDERS		
Hypogonadism*	16	0.785[1]
EYE DISORDERS		
Visual impairment*	8	0.306
GASTROINTESTINAL DISORDERS		
Diarrhea*	510	19.525
Nausea	269	10.299
Vomiting*	177	6.776
Abdominal pain (upper and lower)*	160	6.126
Gastroenteritis and colitis*	66	2.527
Dyspepsia	53	2.029
Pancreatitis*	45	1.723
Gastroesophageal Reflux Disease (GERD)*	40	1.531
Hemorrhoids	39	1.493
Flatulence	36	1.378
Abdominal distension	34	1.302
Constipation*	26	0.995
Stomatitis and oral ulcer*	24	0.919
Duodenitis and gastritis*	20	0.766
Gastrointestinal hemorrhage including rectal hemorrhage*	13	0.498
Dry mouth	9	0.345
Gastrointestinal ulcer*	6	0.230
Fecal incontinence	5	0.191
GENERAL DISORDERS AND ADMINISTRATION SITE		

Table 2 Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult		
System Organ Class (SOC) and Adverse Reaction	**n**	**%**
CONDITIONS		
Fatigue including asthenia*	198	7.580
HEPATOBILIARY DISORDERS		
Hepatitis including AST, ALT, and GGT increases*	91	3.484
Hepatomegaly	5	0.191
Cholangitis	3	0.115
Hepatic steatosis	3	0.115
IMMUNE SYSTEM DISORDERS		
Hypersensitivity including urticaria and angioedema*	70	2.680
Immune reconstitution syndrome	3	0.115
INFECTIONS AND INFESTATIONS		
Upper respiratory tract infection*	363	13.897
Lower respiratory tract infection*	202	7.734
Skin infections including cellulitis, folliculitis, and furuncle*	86	3.292
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolemia*	192	7.351
Hypertriglyceridemia*	161	6.164
Weight decreased*	61	2.335
Decreased appetite	52	1.991
Blood glucose disorders including diabetes mellitus*	30	1.149
Weight increased*	20	0.766
Lactic acidosis*	11	0.421
Increased appetite	5	0.191
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Musculoskeletal pain including arthralgia and back pain*	166	6.355
Myalgia*	46	1.761
Muscle disorders such as weakness and spasm*	34	1.302
Rhabdomyolysis*	18	0.689
Osteonecrosis	3	0.115
NERVOUS SYSTEM DISORDERS		
Headache including migraine*	165	6.317
Insomnia*	99	3.790
Neuropathy and peripheral neuropathy*	51	1.953
Dizziness*	45	1.723
Ageusia*	19	0.727
Convulsion*	9	0.345
Tremor*	9	0.345
Cerebral vascular event*	6	0.230
PSYCHIATRIC DISORDERS		
Anxiety*	101	3.867
Abnormal dreams*	19	0.727
Libido decreased	19	0.727
RENAL AND URINARY DISRODERS		
Renal failure*	31	1.187
Hematuria*	20	0.766

Table 2 Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult		
System Organ Class (SOC) and Adverse Reaction	**n**	**%**
Nephritis*	3	0.115
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Erectile dysfunction*	34	1.668[1]
Menstrual disorders – amenorrhea, menorrhagia*	10	1.742[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash including maculopapular rash*	99	3.790
Lipodystrophy acquired including facial wasting*	58	2.221
Dermatitis/rash including eczema and seborrheic dermatitis*	50	1.914
Night sweats*	442	1.608
Pruritus*	29	1.110
Alopecia	10	0.383
Capillaritis and vasculitis*	3	0.115
VASCULAR DISORDERS		
Hypertension*	47	1.799
Deep vein thrombosis*	17	0.651
* Represents a medical concept including several similar MedDRA PTs [1] Percentage of male population (N=2,038) [2] Percentage of female population (N=574)		

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy including lopinavir/ritonavir with Grade 3 to 4 laboratory abnormalities are presented in **Table 3 and Table 4**.

Table 3
Grade 3 – 4 Laboratory Abnormalities Reported in ≥2% of Adult Antiretroviral-naïve Patients

		Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	**Limit[1]**	**LPV/r capsules 400/100 mg BID + d4T + 3TC (N=326)**	**Nelfinavir 750 mg TID + d4T + 3TC (N=327)**	**LPV/r capsules 800/200 mg QD + TDF + FTC (N=115)**	**LPV/r capsules 400/100 mg BID + TDF + FTC (N=75)**	**LPV/r capsules BID + d4T + 3TC (N=100)**	**LPV/r tablets QD + TDF + FTC (N=333)**	**LPV/r tablets BID + TDF + FTC (N=331)**
Chemistry	**High**							
Glucose	> 250 mg/dL	2%	2%	3%	1%	4%	0%	1%
Uric acid	> 12 mg/dL	2%	2%	0%	3%	5%	<1%	1%
SGOT/AST[2]	> 180 U/L	2%	4%	5%	3%	10%	1%	2%
SGPT/ALT[2]	>215 U/L	4%	4%	4%	3%	11%	1%	1%
GGT	>300	N/A	N/A	N/A	N/A	10%	N/A	N/a

	U/L							
Total cholesterole	>300 mg/dL	9%	5%	3%	3%	27%	4%	3%
Triglycerides	>750 mg/dL	9%	1%	5%	4%	29%	3%	6%
Amylase	>2 x ULN	3%	2%	7%	5%	4%	N/A	N/A
Lipase	>2 x ULN	NA	NA	NA	NA	NA	3%	5%
Chemistry	**Low**							
Calculated Creatinine Clearance	< 50 mL/min	NA	NA	NA	NA	NA	2%	2%
Hematology	**Low**							
Neutrophils	0.75 x 10^9/L	1%	3%	5%	1%	5%	2%	1%

[1] ULN = upper limit of the normal range; N/A = Not Applicable
[2] Criterion for Study 730 was >5x ULN (AST/ALT)

Table 4
Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

		Study 888 (48 Weeks)		**Study 957[2] and Study 765[3] (84-144 Weeks)**
Variable	**Limit[1]**	**Lopinavir/ ritonavir 400/100 mg BID + NVP + NRTIs (n=148)**	**Investigator – selected protease inhibitor(s) + NVP + NRTIs (n=140)**	**Lopinavir/ritonavir BID + NNRTI + NRTIs (n=127)**
Chemistry	High			
Glucose	>250 mg/dL	1%	2%	5%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%
SGOT/ AST	>180 U/L	5%	11%	8%
SGPT/ ALT	>215 U/L	6%	13%	10%
GGT	>300 U/L	N/A	N/A	29%
Total cholesterol	> 300 mg/dL	20%	21%	39%
Triglycerides	>750 mg/dL	25%	21%	36%
Amylase	> 2 x ULN	4%	8%	8%
Chemistry	Low			

Inorganic phosphorus	<1.5 mg/dL	1%	0%	2%
Hematology	Low			
Neutrophils	0.75 x 10^9/L	1%	2%	4%

[1] ULN = upper limit of the normal range; N/A = Not Applicable
[2] Includes clinical laboratory data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 84 weeks. Patients received lopinavir/ritonavir in combination with NRTIs and efavirenz.
[3] Includes clinical laboratory from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 144 weeks. Patients received lopinavir/ritonavir in combination with NRTIs and nevirapine.

ADR - Pediatric

Treatment-Emergent Adverse Events

Lopinavir/ritonavir has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Dysgeusia, vomiting, and diarrhea were the most commonly reported drug related adverse events of any severity in pediatric patients treated with combination therapy including lopinavir/ritonavir for up to 48 weeks in Study 940. A total of 8 children experienced moderate or severe adverse events at least possibly related to lopinavir/ritonavir. Rash (reported in 3%) was the only drug-related clinical adverse event of moderate to severe intensity observed in greater than or equal to 2% of children enrolled.

Laboratory Abnormalities

The percentages of pediatric patients treated with combination therapy including lopinavir/ritonavir with Grade 3 to 4 laboratory abnormalities are presented in **Table 5**.

Table 5
Grade 3 to 4 Laboratory Abnormalities Reported in Greater Than or Equal to 2% Pediatric Patients

Variable	Limit[+]	LPV/r BID + RTIs (N=100)
Chemistry	**High**	
Sodium	>149 mEq/L	3.0%
Total bilirubin	> 2.9 x ULN	3.0%
SGOT/AST	> 180 U/L	8.0%
SGPT/ALT	> 215 U/L	7.0%
Total cholesterol	> 300 mg/dL or >7.77 mmol/L	3.0%
Amylase	>2.5 x ULN	7.0%[++]
Chemistry	**Low**	
Sodium	< 130 mEq/L	3.0%
Hematology	**Low**	
Platelet count	< 50 x 10^9/L	4.0%

Neutrophils	< 0.40 x 10^9/L	2.0%
[+] ULN = upper limit of the normal range [++] Subjects with Grade 3 to 4 amylase confirmed by elevations in pancreatic amylase		

ADR - Post Marketing Experience

Hepatobiliary disorders : Hepatitis has been reported in patients on lopinavir/ritonavir therapy.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme have been reported.

Cardiac disorders: Bradyarrhythmia has been reported.

Renal and urinary disorders: Nephrolithiasis

OVERDOSAGE

Human experience of acute overdosage with lopinavir/ritonavir is limited. Treatment of overdose with lopinavir/ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with lopinavir/ritonavir. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since lopinavir/ritonavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

PHARMACOLOGIC PROPERTIES

Microbiology

Mechanism of Action

Lopinavir, an inhibitor of the HIV-1 and HIV-2 proteases, prevents cleavage of the *gag-pol* polyprotein, resulting in the production of immature, non-infectious virus.

Antiviral activity in vitro

The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10 to 27 nM (0.006 to 0.017 mcg/mL, 1 mcg/mL equals 1.6 microM) and ranged from 4 to 11 nM (0.003 to 0.007 mcg/mL) against several HIV-1 clinical isolates (n equals 6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 to 289 nM (0.04 to 0.18 mcg/mL), representing a 7-to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in-vitro*.

The selection of resistance to lopinavir/ritonavir in antiretroviral treatment naive patients has not yet been characterized. In a Phase III study of 653 antiretroviral treatment naive patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV greater than 400 copies/mL at week 24, 32, 40 and/or 48 were analyzed. No evidence of genotypic or phenotypic resistance to lopinavir/ritonavir was observed in 37 evaluable lopinavir/ritonavir-treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to lopinavir/ritonavir in antiretroviral treatment naïve pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

Resistance to lopinavir/ritonavir has been noted to emerge in patients treated with other protease inhibitors prior to lopinavir/ritonavir therapy. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (greater than 400 copies/mL) viral RNA following treatment with lopinavir/ritonavir for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least four mutations associated with protease inhibitor resistance immediately prior to lopinavir/ritonavir therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on lopinavir/ritonavir therapy. The assessment of these mutational patterns is under study.

Cross-Resistance

Preclinical Studies

Varying degrees of cross-resistance have been observed among protease inhibitors. The in-vitro activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed greater than 4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed less than 4-fold reduced susceptibility to lopinavir. Isolates with greater than 4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the clinical section below (***Clinical Studies:*** *Antiviral Activity of lopinavir/ritonavir in Patients With Previous Protease Inhibitor Therapy*).

Cross-Resistance During Lopinavir/ritonavir Therapy

Little information is available on the cross-resistance of viruses selected during therapy with lopinavir/ritonavir. Isolates from four patients previously treated with one or more protease inhibitors that developed increased lopinavir phenotypic resistance during lopinavir/ritonavir therapy either remained cross-resistant or developed cross-resistance to ritonavir, indinavir, and nelfinavir. All rebound viruses either remained fully sensitive or demonstrated modestly reduced susceptibility to amprenavir (up to 8.5-fold concurrent with 99-fold resistance to lopinavir). The

rebound isolates from the two subjects with no prior saquinavir treatment remained fully sensitive to saquinavir.

Genotypic correlates of reduced virologic response in antiretroviral-experienced patients initiating a lopinavir/ritonavir-based combination regimen

Virologic response to lopinavir/ritonavir has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. **Table 6** shows the 48-week virologic response (HIV RNA <400 copies/mL) according to the number of the above protease inhibitor resistance mutations at baseline in studies 888 and 765 and study 957 (see below).

Table 6 Virologic Response (HIV RNA <400 copies/mL) at Week 48 by Baseline Number of Protease Substitutions Associated with Reduced Response to Lopinavir/ritonavir

Number of protease inhibitor mutations at baseline[1]	Study 888 (Single protease inhibitor-experienced[2], NNRTI-naïve) n=130	Study 765 (Single protease inhibitor-experienced[3], NNRTI-naïve) n=56	Study 957 (Multiple protease inhibitor-experienced[4], NNRTI-naïve) n=50
0-2	76/103	34/45 (76%)	19/20 (95%)
3-5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	N/A	1/4 (25%)

[1] Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V
[2] 43% indinavir, 42% nelfinavir, 10% ritonavir, 15% saquinavir
[3] 41% indinavir, 38% nelfinavir, 4% ritonavir, 16% saquinavir
[4] 86% indinavir, 54% nelfinavir, 80% ritonavir, 70% saquinavir

Table 7 shows the 48-week virologic response (HIV-1 RNA <50 copies/mL) in study 802 according to the number of lopinavir-associated resistance mutations listed in **Table 6** present at baseline. There are insufficient data to support once daily administration of lopinavir/ritonavir for adult patients with three or more lopinavir-associated mutations.

Table 7
Virologic Response (HIV-1 RNA < 50 copies/mL) at Week 48 by Baseline Number of Protease Substitutions Associated with Reduced Response to Lopinavir/ritonavir

Number or protease inhibitor substitutions at baseline[1]	Study 802 (Treatment-experienced[2]) LPV/r Once Daily + NRTIs n=268	Study 802 (Treatment-experienced[3]) LPV/r Twice Daily + NRTIs n=264
0-2	197/255 (65%)	154/250 (62%)
3-5	4/13 (31%)	8/14 (57%)
6 or more	N/A	N/A

[1] Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V
[2] 88% NNRTI-experienced, 47% PI-experienced (24% nelfinavir, 19% indinavir, 13% atazanavir).
[3] 81% NNRTI-experienced, 45% PI-experienced (20% nelfinavir, 17% indinavir, 13% atazanavir).

Clinical Studies

Antiviral Activity of Lopinavir/ritonavir in Patients With Previous Protease Inhibitor Therapy

The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to lopinavir/ritonavir therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naive patients with HIV RNA greater than 1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir, and ritonavir (Study M98-957). In this study, patients were initially randomized to receive one of two doses of lopinavir/ritonavir in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC50 values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC50.against wild-type HIV. Fifty-five percent (31/56) of these baseline isolates displayed a greater than 4-fold reduced susceptibility to lopinavir. These 31 isolates had a mean reduction in lopinavir susceptibility of 27.9-fold.

After 48 weeks of treatment with lopinavir/ritonavir, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA less than or equal to 400 copies/mL was observed in 93% (25/27), 73% (11/15), and 25% (2/8) of patients with less than or equal to 10-fold, greater than 10 and less than 40 fold, and greater than or equal to 40-fold reduced susceptibility to lopinavir at baseline, respectively. Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic. Plasma HIV RNA less than or equal to 50 copies/mL was observed in 81% (22/27), 60% (9/15), and 25% (2/8) in the above groups of patients, respectively.

There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on lopinavir/ritonavir therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

Pharmacokinetic Properties

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of lopinavir/ritonavir 400/100 mg BID yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg BID. The *in vitro* antiviral EC50 of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of lopinavir/ritonavir is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir capsules after lopinavir/ritonavir 400/100 mg BID with food for three weeks from a pharmacokinetic study in HIV-infected adult subjects (n=19).

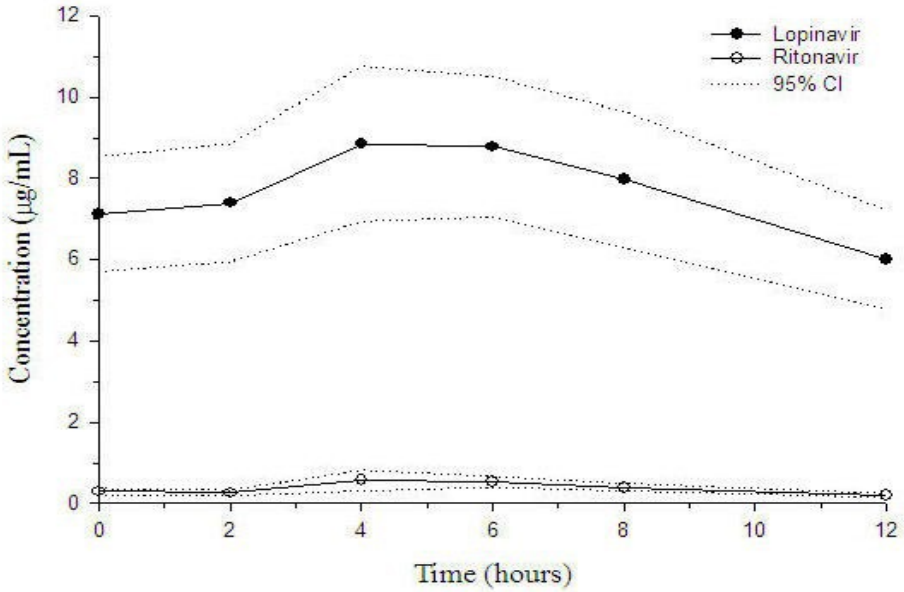


Figure 1 Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (N=19)

Absorption

Tablets

In a pharmacokinetic study in HIV-positive subjects (n=18), multiple dosing with 400/100 mg lopinavir/ritonavir BID with or without food for two weeks produced a mean ± SD lopinavir C_{max} of 12.3 ± 5.4 mcg/mL, occurring approximately four hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 mcg/mL and minimum concentration within a dosing interval was 5.6 ± 4.5 mcg/mL. Lopinavir AUC over a 12-hour dosing interval averaged 113.2 ± 60.5 mcg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg tablets are equivalent to three 133/33 mg capsules under fed conditions with less pharmacokinetic variability.

Effects of Food on Oral Absorption

Tablets

Administration of a single 400/100 mg dose of lopinavir/ritonavir tablets under fed conditions (high-fat, 872 kcal, 56% from fat) compared to the fasted state was associated with no significant changes in Cmax and AUC, therefore, lopinavir/ritonavir tablets may be taken with or without food. Lopinavir/ritonavir tablets have also shown less pharmacokinetic variability under all meal conditions compared to the lopinavir/ritonavir capsule.

Distribution

At steady state, lopinavir is approximately 98 to 99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin, however, it has a higher affinity for AAG.

At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg lopinavir/ritonavir BID, and is similar between healthy volunteers and HIV-positive patients.

Metabolism

In vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor, which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg lopinavir/ritonavir dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Excretion

Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after eight days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5.98 +/- 5.75 L/hr (mean +/- SD, N=19).

Pharm - PK - Pediatric

The pharmacokinetics of lopinavir/ritonavir 300/75 mg/m^2 BID and 230/57.5 mg/m^2 BID have been studied in a total of 53 pediatric patients, ranging in age from six months to 12 years. The 230/57.5 mg/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine). Lopinavir/ritonavir once daily has not been evaluated in pediatric patients.

The lopinavir mean steady-state AUC, $_{Cmax,}$ and C_{min} were 72.6 ± 31.1mcg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 mcg/mL, respectively after lopinavir/ritonavir 230/57.5 mg/m2 BID without nevirapine (n=12), and were 85.8 ± 36.9 mcg•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5 mcg/mL, respectively after 300/75 mg/m2 BID with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BID (six months to eight years) or 4 mg/kg BID (greater than eight years).

Once Daily Dosing

The pharmacokinetics of once daily lopinavir/ritonavir have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Lopinavir/ritonavir 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once daily regimen. Multiple dosing of 800/200 mg lopinavir/ritonavir once daily for 2 weeks without meal restriction (n = 16) produced a mean ± SD lopinavir C_{max} of 14.8 ± 3.5µg/mL, occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 5.5 ± 5.4 µg/mL and minimum concentration within a dosing interval was 3.2 ± 3.4 µg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 206.5 ± 89.7 µg•h/mL.

Effects on Electrocardiogram

QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once-daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) differences in QTcF from placebo were 3.6 (6.3) msec and 13.1(15.8) msec for 400/100 mg twice-daily and supratherapeutic 800/200 mg twice-daily lopinavir/ritonavir, respectively. The two regimens resulted in exposures on Day 3 that were approximately 1.5 and 3-fold higher than those observed with recommended once-daily or twice-daily lopinavir/ritonavir doses at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving lopinavir/ritonavir in the same study on Day 3. Maximum PR interval was 286 msec and no second or third degree heart block was observed (see **WARNINGS AND PRECAUTIONS**).

Special Populations

Gender, Race and Age

Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Pharm - Renal Impairment

Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Pharm - Hepatic Impairment

Lopinavir is principally metabolized and eliminated by the liver. Multiple dosing of lopinavir/ritonavir 400/100 mg twice daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment resulted in a 30% increase in lopinavir AUC and 20% increase in Cmax compared to HIV–infected subjects with normal hepatic function. Additionally, the plasma protein binding of lopinavir was lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31% respectively). Lopinavir/ritonavir has not been studied in patients with severe hepatic impairment (see PRECAUTIONS).

Drug-Drug Interactions

(See also **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS**: ***Drug Interactions*** **and DRUG INTERACTIONS)**

Lopinavir/ritonavir is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of lopinavir/ritonavir and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS**).

Lopinavir/ritonavir does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

Lopinavir/ritonavir has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

Lopinavir/ritonavir is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, co-administration of lopinavir/ritonavir and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with lopinavir/ritonavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of lopinavir/ritonavir on the AUC, C_{max} and C_{min} are summarized in **Table 8** (effect of other drugs on lopinavir) and **Table 10** (effect of lopinavir/ritonavir on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see **DRUG INTERACTIONS**.

Table 8
Drug Interactions
Pharmacokinetic Paramenters for Lopinavir in the Presece of the Co-administered Drug (see DRUG INTERACTIONS for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Lopinavir/ritonavir (mg)	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	750 BID, 10 d	400/100 capsule BID, 21 d	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Boceprevir	800 mg q8h, 6 d	400/100 tablet BID, 22 d	39	0.70 (0.65, 0.77)	0.66 (0.60, 0.72)	0.57 (0.49, 0.65)
Efavirenz[1]	600 QHS, 9 d	400/100 capsule BID, 9 d	11.7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 QHS, 9 d	500/125 tablet BID, 10 d	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)

	600 QHS, 9 d	600/150 tablet BID, 10 d	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Ketoconazole	200 single dose	400/100 capsule BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 BID, 10 d	400/100 capsule BID, 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 BID, steady state (>1yr)[2]	400/100 capsule BID, steady state (>1yr)	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID, 1 wk	300/75 oral solution mg/m^2 BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Omeprazole	40 QD, 5 d	400/100 tablet BID, 10 d	12	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.003 (0.90, 1.18)
		800/2011 tablet QD, 10 d	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
Pravastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Ranitidine	150 single dose	400/100 tablet BID, 10 d	12	0.98 (0.95, 1.02)	0.98 (0.94, 1.01)	0.93 (0.89, 0.98)
		800/200 tablet QD, 10 d	11	0.98 (0.95, 1.01)	0.96 (0.90, 1.02)	0.85 (0.67, 1.08)
Rifabutin	150 QD, 10 d	400/100 capsule BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampin	600 QD, 10 d	400/100 capsule BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 QD, 14 d	800/200 capsule BID, 9 d[4]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 QD, 14 d	400/400 capsule BID, 9 d[5]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
					Co-administration of standard dose lopinavir/ritonavir and rifampin is not recommended (see DRUG INTERACTIONS)	
Ritonavir[2]	100 BID, 3 to 4	400/100 capsule BID, 3	8,	1.28	1.46	2.16

	wk	to 4 wk	21*	(0.94, 1.76)	(1.04, 2.06)	(1.29, 3.62)
Telaprevir	750 mg q8h for 10 days	400/100 BID for 20 days	12	0.96 (0.87, 1.05)	1.06 (0.96, 1.17)	1.14 (0.96, 1.36)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

1. The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz
2. Study conducted in HIV-positive adult subjects
3. Study conducted in HIV-positive pediatric subjects ranging in age from 6 moths to 12 years
4. Titrated to 800/200 BID as 533/133 BID x 1 d, 667/167 BID x 1 d, then 800/200 BID x 7 d, compared to 400/100 BID x 10 days alone
5. Tiitrated to 400/400 BID as 400/200 BID x 1 d, 400/300 BID x 1 d, then 400/400 BID x 7 d, compared to 400/100 BID x 10 days

* Parallel group design; n for lopinavir/ritonavir + co-administered drug, n for lopinavir/ritonavir alone

Table 9
Drug Interactions
Pharmacokinetic Parameters for Co-administered Drug in the Presence of Lopinavir/ritonavir
(see DRUG INTERACTIONS for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Lopinavir/ritonavir (mg)	n	Ratio (with/without Lopinavir/ritonavir) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir[1]	750 BID, 10 d combo vs. 1200 BID, 14 d alone	400/100 capsule BID, 21 d	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Atorvastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Boceprevir	800 mg q8h, 6 d	400/100 tablet BID, 22 d	39	0.50 (0.45, 0.55)	0.55 (0.49, 0.61)	0.43 (0.36, 0.53)
Desipramine[2]	100 single dose	400/100 capsule BID, 10 d	15	0.91 (0.84, 0.7)	1.05 (0.96, 1.16)	NA
Efavirenz	600 QHS, 9 d	400/100 capsule BID, 9 d	11,12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 mcg QD, 21 d (Ortho Novum®)	400/100 capsule BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir[1]	600 BID, 10 d combo	400/100 capsule BID, 15 d	13	0.71 (0.63,	0.91 (0.75,	3.47 (2.60,

	nonfasting vs. 800 TID, 5 d alone fasting			0.81)	1.10)	4.64)
Ketoconazole	200 single dose	400/100 capsule BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	NA
Lamotrigine	100 BID, 12 d vs. 100 BID, 8 d alone	400/100 capsule BID, 12 d	18	0.54 (0.49, 0.58)	0.5 (0.47, 0.54)	0.44 (0.40, 0.47)
	200 BID, 9 d vs. 100 BID, 8 d alone	400/10 capsule BID, 9 d	15	1.03 (0.90, 1.17)	0.91 (0.82, 1.02)	0.79 (0.69, 0.90)
Maraviroc	300 mg BID	400/100 capsule BID	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)
Methadone	5 single dose	400/100 capsule BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	NA
Nelfinavir[1] MS metabolite	1000 BID, 10 d combo vs. 1250 BID, 14 d alone	400/100 capsule BID, 21 d	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)
				2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)
Nevirapine	200 QD, 14 d; BID, 6 d	400/100 capsule BID, 20 d	5,6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho Novum®)	400/100 capsule BID, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	NA
Rifabutin 25-O-desacetyl rifabutin Rifabutin+ 25-O-desacetyl rifabutin[3]	150 QD, 10 d combo vs. 300 QD, 10 d; alone	400/100 capsule BID, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Telaprevir	750 mg q8h for 10 days	400/100 BID for 20 days	12	0.47 (0.41, 0.52)	0.46 (0.41, 0.52)	0.48 (0.40, 0.56)
Saquinavir[1]	800 BID, 10 d combo vs. 100 TID, 5 d alone	400/100 capsule BID, 15 d	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
	1200 BID, 5 d combo vs.	400/100 capsule BID, 20 d	10	6.44 (5.59,	9.91 (8.28,	16.54 (10.91,

	1200 TID, 5 d alone			7.41)	11.86)	25.08)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] Ratio of parameters for amprenavir, indinavir, nelfinavir, and saquinavir are not normalized for dose.
[2] Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism
[3] Effect on the dose-normalized sum of rifabutin parent and 25-O-desaceyl rifabutin active metabolite
* Parallel group design; n for lopinavir/ritonavir + co-administered drug, n for co-administered drug alone.
NA = not available

PRE-CLINICAL SAFETY DATA

Acute, Subacute and Chronic Toxicity

Repeat-dose toxicity studies in rodents and dogs identified major target organs as the liver, kidney, thyroid, spleen and circulating red blood cells. Hepatic changes indicated cellular swelling with focal degeneration. While exposure eliciting these changes were comparable to human clinical exposure, dosages in animals were over 6-fold the recommended clinical dose. Mild renal tubular degeneration was confined to mice exposed with at least twice the recommended human exposure; the kidney was unaffected in rats and dogs. Reduced serum thyroxine led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs. Enlarged spleens with histiocytosis were seen in rats but not other species. Serum cholesterol was elevated in rodents but not dogs, while triglycerides were elevated only in mice.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies of lopinavir/ritonavir in mice revealed a non-genotoxic, mitogenic induction of liver tumors, generally considered to have little relevance to human risk. Carcinogenicity studies in rats revealed no tumorigenic findings. Lopinavir was not found to be mutagenic or clastogenic in a battery of *in vitro* assays including the Ames bacterial reverse mutation assay, the mouse lymphoma assay, and chromosomal aberration assays in human lymphocytes. Lopinavir/ritonavir was not found to be mutagenic or clastogenic in *in vivo* assays using the mouse micronucleus assay.

DESCRIPTION OF CLINICAL STUDIES

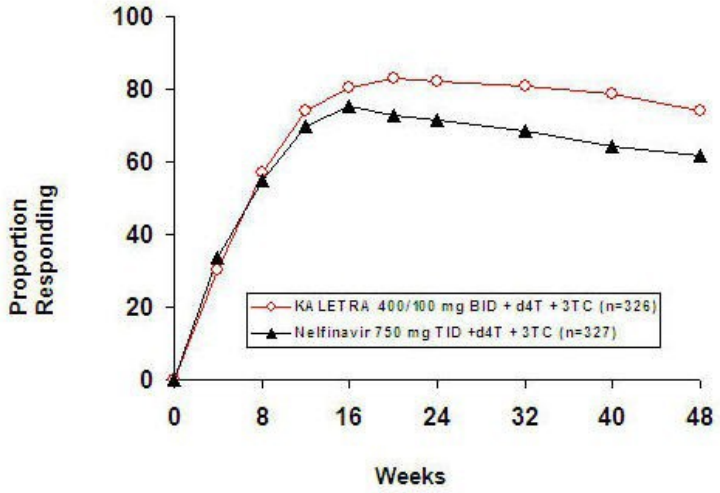
Patients without Prior Antiretroviral Therapy

Study M98-863: Lopinavir/ritonavir Capsules BID + stavudine + lamivudine compared to nelfinavir TID + stavudine + lamivudine.

Study M98-863 is an ongoing, randomized, double-blind, multicenter trial comparing treatment with lopinavir/ritonavir capsules (400/100 mg BID) plus stavudine and lamivudine versus nelfinavir (750 mg TID) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80%

were male. Mean baseline CD4 cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 2.6 to 6.8 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment are presented in **Figure 2** and **Table 10**, respectively.



*Proportion of patients at each time point who have achieved and maintained HIV RNA less than 400 copies/mL, are on their original study medication, and have not experienced a new CDC Class C event.

Table 10
Outcomes of Randomized Treatment Through Week 48 (Study 863)

Outcome	Lopinavir/ritonavir + d4T + 3TC (N=326)	Nelfinavir + d4T + 3TC (N=327)
Responder*[1]	75%	62%
Virologic failure[2] Rebound Never suppressed through Week 48	9% 7% 2%	25% 15% 9%
Death	2%	1%
Discontinued due to adverse event	4%	4%
Discontinued for other reasons[3]	10%	8%

* Corresponds to rates at Week 48 in Figure 3

[1] Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48

[2] Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48

[3] Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through Week 48, including patients who discontinued subsequent to virologic failure, was 17% in the lopinavir/ritonavir arm and 24% in the nelfinavir arm.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the lopinavir/ritonavir arm compared to the nelfinavir arm with HIV RNA less than 400 copies/

mL (75% vs. 62%, respectively) and HIV RNA less than 50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV RNA level subgroups is presented in **Table 11**.

Table 11
Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)

Baseline Viral Load (HIV-1 RNA copies/mL)	Lopinavir/ritonavir + d4T + 3TC			Nelfinavir + d4T + 3TC		
	<400 copies/mL[1]	<50 copies/ mL[2]	n	<400 copies/mL[1]	<50 copies/ mL[2]	n
<30,000	74%	71%	82	79%	72%	87
=30,000 to <100,000	81%	73%	79	67%	54%	79
=100,000 to <250,000	75%	64%	83	60%	47%	72
=250,000	72%	60%	82	44%	33%	89

[1] Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48
[2] Patients achieved HIV RNA <50 copies/mL at Week 48

Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was 207 cells/mm^3 for the lopinavir/ritonavir arm, and 195 cells/mm^3 for the nelfinavir arm.

Figure 3 displays the Kaplan-Meier estimates of the time to treatment failure in Study 863. The time of treatment failure was defined as the earliest time a patient experienced virologic failure (two consecutive HIV RNA values demonstrating rebound above 400 copies/mL), a new CDC Class C event, or premature discontinuation from the study.

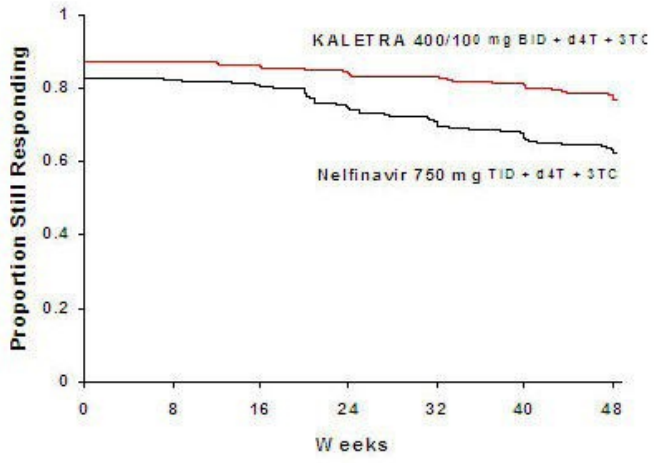


Figure 3 Time to Treatment Failure (Study 863)

Study M97-720: Lopinavir/ritonavir BID + stavudine + lamivudine

Study M97-720 was a randomized, blinded, multicenter trial evaluating treatment with lopinavir/ritonavir at three dose levels (Group I: 200/100 mg BID and 400/100 mg BID; Group II:

400/100 mg BID and 400/200 mg BID) plus lamivudine (150 mg BID) and stavudine (40 mg BID) in 100 patients. All patients were converted to open label lopinavir/ritonavir at the 400/100 mg BID dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 70% were Caucasian, and 96% were male. Mean baseline CD4 cell count was 338 cells/mm^3 (range: 3 to 918 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 3.3 to 6.3 $\log_{10}$ copies/mL).

Through 360 weeks of treatment in study 720, the proportion of patients with HIV RNA less than 400 (less than 50) copies/mL was 61% (59%) [n=100], and the corresponding mean increase in CD_4 cell count was 501 cells/mm^3. Thirty-nine patients (39%) discontinued the study, including 15 (15%) discontinuations due to adverse events and 1 (1%) death. 18 patients demonstrated loss of virologic response (two consecutive rebound HIV-1 RNA values above 400 copies/mL, one rebound HIV-1 RNA value followed by discontinuation, or failure to achieve HIV RNA <400 copies/ml. Genotypic analysis of viral isolates was conducted on these patients and 10 additional patients with isolated HIV-1 RNA values >400 copies/mL after week 24. Results were available from 19 patients and confirmed no primary or active site mutations in protease (amino acids at positions 8, 30, 32, 36, 47, 48, 50, 82, 84 and 90) or protease inhibitor phenotypic resistance.

Study 418: Lopinavir/ritonavir capsules once daily + tenofovir DF + emtricitabine compared to lopinavir/ritonavir twice daily + tenofovir DF + emtricitabine

Study 418 was a randomized, open-label, multicenter trial comparing treatment with lopinavir/ritonavir capsules 800/200 mg once-daily plus tenofovir DF and emtricitabine versus lopinavir/ritonavir capsules 400/100 mg twice-daily plus tenofovir DF and emtricitabine in 190 antiretroviral treatment naïve patients.

Patients had a mean age of 39 years (range: 19 to 75), 54% were Caucasian, and 78% were male. Mean baseline CD_4 cell count was 260 cells/mm^3 (range: 3 to 1006 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL (range: 2.6 to 6.4 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment are presented in **Table 12**.

Table 12
Outcomes of Randomized Treatment Through Week 48 (Study 418)

Outcome	Lopinavir/ritonavir once daily + TDF + FTC (n=115)	Lopinavir/ritonavir twice daily + TDF + FTC (n=75)
Responder[1]	71%	65%
Virologic failure[2] Rebound Never suppressed through Week 48	10% 6% 3%	9% 5% 4%
Death	0%	1%
Discontinued due to an adverse event	12%	7%
Discontinued for other reasons[3]	7%	17%

[1] Patients achieved and maintained confirmed HIV RNA <50 copies/mL through Week 48
[2] Includes confirmed viral rebound and failure to achieve confirmed <50 copies/mL through Week 48
[3] Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other

reasons

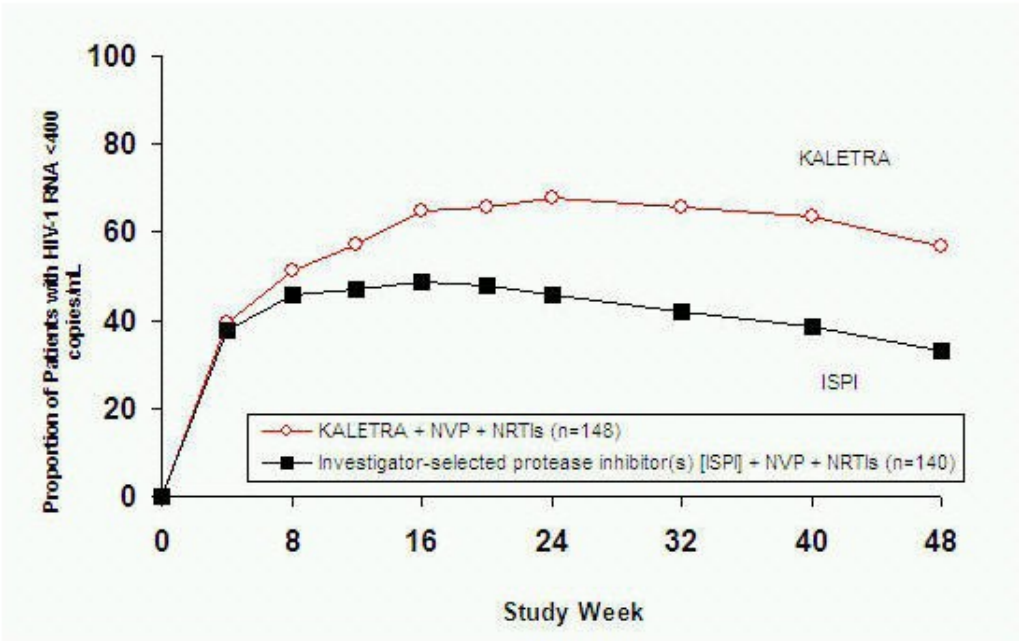
Through 48 weeks of therapy, 71% in the lopinavir/ritonavir once daily arm and 65% in the lopinavir/ritonavir twice daily arm achieved and maintained HIV RNA < 50 copies/mL (95% confidence interval for the difference, -7.6% to 19.5%). Mean CD_4 cell count increases at Week 48 were 185 cells/mm^3 for the lopinavir/ritonavir once daily arm, and 196 cells/mm^3 for the lopinavir/ritonavir twice daily arm.

Patients with Prior Antiretroviral Therapy

Study M98-888: Lopinavir/ritonavir capsules BID + nevirapine + NRTIs compared to investigator-selected protease inhibitor(s) + nevirapine + NRTIs

Study 888 was a randomized, open- label, multicenter trial comparing treatment with lopinavir/ritonavir capsules (400/100 mg BID) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naive patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD_4 cell count was 322 cells/mm^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 log_{10} copies/mL (range: 2.6 to 6.0 log_{10} copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in **Figure 4** and **Table 14** respectively.



* Roche AMPLICOR HIV-1 MONITOR Assay

† Responders at each visit are patients who had achieved and maintained HIV-1 RNA <400 copies/mL without discontinuation by that visit.

Table 14
Outcomes of Randomized Treatment Through Week 48 (Study 888)

Outcome	Lopinavir/ritonavir + nevirapine + NRTIs (n=148)	Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n=140)
Responder*[1]	57%	33%
Virologic Failure[2]	24%	41%
Rebound	11%	19%
Never suppressed through Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons[3]	14%	13%

* Correspons to rates at Week 48 in Figure 5

[1] Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

[2] Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48

[3] Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Study M97-765: Lopinavir/ritonavir Capsules BID + nevirapine + NRTIs

Study M97-765 was a randomized, blinded, multicenter trial evaluating treatment with lopinavir/ritonavir capsules at two dose levels (400/100 mg BID and 400/200 mg BID) plus nevirapine (200 mg BID) and two NRTIs in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients. Patients had a mean age of 40 years (range 22 to 66), were 73% Caucasian, and were 90% male. Mean baseline CD_4 cell count was 372 cells/mm^3 (range 72 to 807 cells/mm3) and mean baseline-plasma HIV-1 RNA was 4.0 log_{10} copies/mL (range 2.9 to 5.8 log_{10} copies/mL).

Through 144 weeks of treatment in study 765, the proportion of patients with HIV RNA less than 400 (less than 50) copies/mL was 54% (50%) [n=70], and the corresponding mean increase in CD_4 cell count was 212 cells/mm^3. 27 patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

Pediatric Use

KONCERT/PENTA 18: Kaletra Once Daily Randomized Trial of the Pharmacokinetics, Safety and Efficacy of Twice Daily versus Once Daily Lopinavir/Ritonavir Tablets Dosed by Weight as Part of Combination Antiretroviral Therapy in HIV-1 Infected Children/Paediatric European Network for the Treatment of AIDS

KONCERT/PENTA18 is a prospective multicenter, randomized, open-label study that evaluated the pharmacokinetic profile, efficacy, and safety of twice-daily versus once-daily dosing of lopinavir/ritonavir 100/25 mg tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included lopinavir/ritonavir, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, the efficacy and safety with twice daily dosing (n=87) in the

pediatric population given lopinavir/ritonavir 100/25 mg tablets was consistent with the efficacy and safety findings in previous adult and pediatric studies using lopinavir/ritonavir twice daily.

STORAGE

Store below 30°C. Shelf life 3 years.

HOW SUPPLIED

200/50 mg Red tablets:

Aluvia (lopinavir/ritonavir) tablets are red, film-coated tablets debossed with the Abbott logo and the Abbo-Code AL. Lopinavir/ritonavir is available as 200 mg lopinavir/50 mg ritonavir tablets.

Pack: Plastic Bottle @ 120 film coated tablet

Reg. No.:

HARUS DENGAN RESEP DOKTER

Manufactured by:
AbbVie Deutschland GmbH & Co KG.
Knollstrasse, Ludwigshafen, Germany 67061

Registered by:
PT. Pyridam Farma Tbk.
Cianjur / INDONESIA