

Lopinavir and Ritonavir tablets
LOPIMUNE

COMPOSITION

LOPIMUNE Tablets

Each film-coated tablet contains

Lopinavir 200 mg

Ritonavir 50 mg

DOSAGE FORM

Oral, Film coated tablets

DESCRIPTION

LOPIMUNE is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 protease. As co-formulated in **LOPIMUNE**, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

PHARMACOLOGY

Pharmacodynamics

Lopinavir is a potent inhibitor of HIV-protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

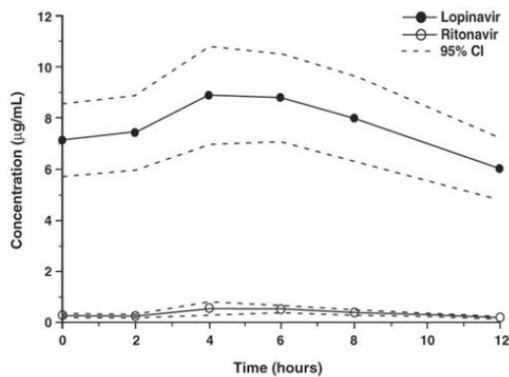
Pharmacokinetics

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-1 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 twice-daily yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-1 infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg twice-daily.

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 after lopinavir/ritonavir 400/100 mg twice-daily with food for 3 weeks from a pharmacokinetic study in HIV-1 infected adult subjects (n =19).

Fig1. Mean Steady-state Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-1 Infected Adult Subjects (N = 19)



Absorption

In a pharmacokinetic study in HIV-1 positive subjects (n = 19), multiple dosing with 400/100 mg lopinavir/ritonavir twice-daily with food for 3 weeks produced a mean \pm SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 $\mu\text{g/mL}$, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 $\mu\text{g/mL}$ and minimum concentration within a dosing interval was 5.5 ± 2.7 $\mu\text{g/mL}$. Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 $\mu\text{g}\cdot\text{h/mL}$. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of lopinavir/ritonavir co-formulated capsules and oral solution. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the lopinavir/ritonavir oral solution relative to the capsule formulation.

Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg lopinavir/ritonavir tablets are similar to three 133.3/33.3 mg lopinavir /ritonavir capsules under fed conditions with less pharmacokinetic variability.

Effects of Food on Oral Absorption:

No clinically significant changes in C_{max} and AUC were observed following administration of lopinavir/ritonavir tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of lopinavir/ritonavir tablets with a moderate fat meal (500 –682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 26.9% and 17.6%, respectively. Relative to fasting, administration of lopinavir/ritonavir tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9%, but not C_{max} . Therefore, lopinavir/ritonavir tablets may be taken with or without food.

Distribution

At steady state, lopinavir is approximately 98-99% 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 twice daily, and is similar between healthy volunteers and HIV-1 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 ¹⁴C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg lopinavir/ritonavir dose was due to the 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.

Elimination

Following a 400/100 mg ¹⁴C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ¹⁴C-lopinavir can be accounted for in urine and feces, respectively, after 8 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).

Once-Daily Dosing

The pharmacokinetics of once-daily lopinavir/ritonavir have been evaluated in HIV-1 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 4 weeks with food (n = 24) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 11.8 ± 3.7 µg/mL, occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 3.2±2.1 µg/mL and minimum concentration within a dosing interval was 1.7 ± 1.6µg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 154.1 ± 61.4 µg• h/mL. The pharmacokinetics of once daily lopinavir/ritonavir has also been evaluated in treatment experienced HIV-1 infected subjects. Lopinavir exposure (C_{max}, AUC(0-24h), C_{trough}) with once daily lopinavir/ritonavir administration in treatment experienced subjects is comparable to the once daily lopinavir exposure in treatment naïve subjects.

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 time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction were 5.3 (8.1) and 15.2 (18.0) mseconds (msec) for 400/100 mg twice daily and suprathapeutic 800/200 mg twice daily lopinavir/ritonavir, respectively. Lopinavir/ritonavir 800/200 mg twice daily resulted in a Day 3 mean C_{max} approximately 2-fold higher than the mean C_{max} observed with the approved once daily and twice daily lopinavir/ritonavir doses at steady state. PR interval prolongation was also noted in subjects receiving lopinavir/ritonavir in the same study on Day 3.

The maximum mean (95% upper confidence bound) difference from placebo in the PR interval after baseline-correction were 24.9 (21.5, 28.3) and 31.9 (28.5, 35.3) msec for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily lopinavir/ritonavir, respectively. (see **WARNINGS AND PRECAUTIONS**).

Special Populations

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.

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 (n = 12) resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV-infected subjects with normal hepatic function (n = 12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31%, respectively).

Caution should be exercised when administering **LOPIMUNE** to subjects with hepatic impairment. Lopinavir/ritonavir has not been studied in patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

INDICATIONS

LOPIMUNE is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with

LOPIMUNE:

- The use of other active agents with **LOPIMUNE** is associated with a greater likelihood of treatment response (see **PHARMACOLOGY**).
- Genotypic or phenotypic testing and/or treatment history should guide the use of **LOPIMUNE** (see **PHARMACOLOGY**). The number of baseline primary protease inhibitor mutations affects the virologic response to **LOPIMUNE** (see **PHARMACOLOGY**).
- Once-daily administration of **LOPIMUNE** is not recommended for therapy-experienced adult patients or any pediatric patients.

DOSAGE AND ADMINISTRATION

LOPIMUNE tablets may be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

Adult Patients

Therapy-Naive Patients:

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

LOPIMUNE tablets 800/200 mg (given as four 200/50 mg tablets) once-daily taken with or without food.

Therapy-Experienced Patients:

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

Lopinavir/ritonavir tablets 800/200 mg (given as four 200/50 mg tablets) once daily in patients with less than three lopinavir resistance-associated substitutions.

Once daily administration of **LOPIMUNE** is not recommended for adult patients with three or more of the following lopinavir resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

LOPIMUNE should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin (see *Drug Interactions*)

Concomitant Therapy: Efavirenz, nevirapine, (fos)amprenavir or nelfinavir: (see **WARNINGS AND PRECAUTIONS: Drug interactions**)

LOPIMUNE tablets should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, (fos)amprenavir or nelfinavir.

- A dose increase is recommended for all patients who use **LOPIMUNE** tablets. The recommended dose of **LOPIMUNE** tablets is 500/125 mg (such as two 200/50 tablets and one 100/25 mg tablet) twice daily in combination with efavirenz, nevirapine, (fos)amprenavir or nelfinavir.

Pediatrics patients

LOPIMUNE tablets should not be administered once-daily in pediatric patients < 18 years of age.

Healthcare professionals should pay special attention to accurate calculation of the dose of **LOPIMUNE**, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors, overdose, (see **OVERDOSAGE**) and underdose.

Prescribers should calculate the appropriate dose of **LOPIMUNE** for each individual child based on body weight (kg) or body surface area (BSA) and should not exceed the recommended adult dose.

Body surface area (BSA) can be calculated as follows:

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

The **LOPIMUNE** dose can be calculated based on weight or BSA:

Based on Weight: Patient Weight (kg) × Prescribed lopinavir dose (mg/kg) = Administered lopinavir dose (mg)

Based on BSA: Patient BSA (m²) × Prescribed lopinavir dose (mg/m²) = Administered lopinavir dose (mg)

Before prescribing **LOPIMUNE** 200/50 mg tablets, children should be assessed for the ability to swallow intact tablets. If a child is unable to reliably swallow a **LOPIMUNE** tablet, an alternate formulation should be prescribed.

6 Months to 18 Years:

Without Concomitant Efavirenz, Nevirapine, (Fos)amprenavir or Nelfinavir:

If weight-based dosing is preferred, the recommended dosage of lopinavir/ritonavir for patients < 15 kg is 12/3 mg/kg given twice daily and the dosage for patients ≥ 15 kg to 40 kg is 10/2.5 mg/kg given twice daily.

Concomitant Therapy: Efavirenz, Nevirapine, (Fos)amprenavir, or Nelfinavir

A dose increase of lopinavir to 300/75 mg/m² is needed when co-administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir in children (both treatment-naive and treatment-experienced) 6 months to 18 years of age, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage for patients <15 kg is 13/3.25 mg/kg given twice daily and the dosage for patients >15 kg to 45 kg is 11/2.75 mg/kg given twice daily.

Table 1 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on body weight or body surface area for **LOPIMUNE** tablets when given in combination with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir.

Table 1. Pediatric Dosing Recommendations for Patients 6 Months to 18 Years of Age Based on Body Weight or Body Surface Area for LOPIMUNE Tablets With Concomitant Efavirenz[†], Nevirapine, (Fos)amprenavir[†] or Nelfinavir[†]

Body Weight (kg)	Body Surface Area (m ²)*	Recommended number of 100/25 mg Tablets Twice Daily
15 to 25	≥0.6 to < 0.9	2
>25 to 35	≥0.9 to < 1.4	3
>35	≥1.4	4 (or two 200/50 mg tablets)

*Lopinavir/ritonavir oral solution is available for children with a BSA less than 0.6 m² or those who are unable to reliably swallow a tablet.

CONTRAINDICATIONS

LOPIMUNE is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g. Stevens-Johnson syndrome, erythema multiforme) to any of its ingredients, including ritonavir.

Co-administration of **LOPIMUNE** is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions.

Co-administration of **LOPIMUNE** is contraindicated with potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance. These drugs are listed in Table 2.

Table: 2 Drugs That Are Contraindicated With LOPIMUNE

Drug Class	Drugs Within Class That Are Contraindicated With LOPIMUNE	Clinical comments
Alpha 1-Adrenoreceptor antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antimycobacterial	Rifampin	May lead to loss of virologic response and possible resistance to LOPIMUNE or to the class of protease inhibitors or other co-administered antiretroviral agents. (see WARNINGS AND PRECAUTIONS)
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylethergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.

GI motility agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St Johns wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to LOPIMUNE or to the class of protease inhibitors.
PDE5 enzyme inhibitor	Sildenafil ^a when used for the treatment of pulmonary arterial hypertension	A safe and effective dose has not been established when used with lopinavir/ritonavir. There is an increased potential for sildenafil-associated adverse events including visual abnormalities, hypotension, prolonged erection, and syncope) (see Drug Interactions).
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias
Sedative/Hypnotics	Triazolam; orally administered midazolam ^b	Prolonged or increased sedation or respiratory depression

^a See Drug Interactions for co-administration of sildenafil in patients with erectile dysfunction.

^b See Drug Interactions, Table 3 for parenterally administered midazolam

WARNINGS AND PRECAUTIONS

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 are a risk factor for development of pancreatitis (see **WARNINGS AND PRECAUTIONS**). Patients with advanced HIV-1 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 **LOPIMUNE** therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and **LOPIMUNE** and/or other antiretroviral therapy should be suspended as clinically appropriate.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-1 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.

PR Interval Prolongation

Lopinavir/ritonavir prolongs the PR interval in some patients. Cases of second or third degree atrioventricular block have been reported. **LOPIMUNE** should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.

The impact on the PR interval of co-administration of lopinavir/ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of **LOPIMUNE** with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended. (see **PHARMACOLOGY**).

QT Interval Prolongation

Postmarketing cases of QT interval prolongation and torsade de pointes have been reported although causality of lopinavir/ritonavir could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval (see **PHARMACOLOGY**)

Hepatotoxicity

Patients with underlying hepatitis B or C or marked elevations in transaminase prior to treatment may be at increased risk for developing or worsening of transaminase elevations or hepatic decompensation with use of **LOPIMUNE**.

There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV-1 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.

Appropriate laboratory testing should be conducted prior to initiating therapy with **LOPIMUNE** and patients should be monitored closely during treatment. Increased AST/ALT monitoring should be considered in the patients with underlying chronic hepatitis or cirrhosis, especially during the first several months of **LOPIMUNE** treatment. (see Use in specific populations)

Resistance/Cross-resistance

Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in lopinavir /ritonavir-treated patients, it is unknown what effect therapy with lopinavir/ritonavir will have on the activity of subsequently administered protease inhibitors.

Patients with 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. A causal relationship between protease inhibitor therapy and these events has not been established.

Lipid Elevations

Treatment with lopinavir/ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides (see **UNDESIRABLE EFFECTS**). Triglyceride and cholesterol testing should be performed prior to initiating therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with **LOPIMUNE** and HMG-CoA reductase inhibitors. (see **CONTRAINDICATIONS and DRUG INTERACTIONS**)

Immune Reconstitution Syndrome

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

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.

Drug Interactions

See also **CONTRAINDICATIONS**

Potential for LOPIMUNE to Affect Other Drugs

Lopinavir/ritonavir is an inhibitor of CYP3A and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (>3-fold) when co-administered with lopinavir and ritonavir. Thus, co-administration of **LOPIMUNE** with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious

and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 3. Additionally, **LOPIMUNE** induces glucuronidation.

Potential for Other Drugs to Affect Lopinavir

Lopinavir/ritonavir is a CYP3A substrate; therefore, drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce **LOPIMUNE's** therapeutic effect. Although not observed in the lopinavir/ritonavir /ketoconazole drug interaction study, co-administration of **LOPIMUNE** and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Established and Other Potentially Significant Drug Interactions: Table 3 provides a listing of established or potentially clinically significant drug interactions. Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction.

Table 3. Established and Other Potentially Significant Drug Interactions		
Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz, nevirapine	↓ lopinavir	<p>LOPIMUNE dose increase is recommended in all patients (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY).</p> <p>Increasing the dose of lopinavir/ritonavir tablets to 500/125 mg (given as two 200/50 tablets and one 100/25 mg tablet) twice daily co-administered with efavirenz resulted in similar lopinavir concentrations compared to lopinavir/ritonavir tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz.</p> <p>Increasing the dose of lopinavir/ritonavir tablets to 600/150 mg (given as three 200/50 mg tablets) twice-daily co-administered with efavirenz resulted in significantly higher lopinavir plasma concentrations compared to lopinavir/ritonavir tablets 400/100 mg twice-daily without efavirenz.</p> <p>LOPIMUNE should not be administered once-daily in combination with efavirenz or nevirapine. (See DOSAGE AND ADMINISTRATION and PHARMACOLOGY)</p>
Non-nucleoside	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.

Reverse Transcriptase Inhibitor: delavirdine		
Nucleoside Reverse Transcriptase Inhibitor: didanosine		LOPIMUNE tablets can be administered simultaneously with didanosine without food.
Nucleoside Reverse Transcriptase Inhibitor: tenofovir	↑ tenofovir	Lopinavir and Ritonavir increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving LOPIMUNE and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside Reverse Transcriptase Inhibitor: abacavir zidovudine	↓ abacavir ↓ zidovudine	Lopinavir and Ritonavir induce glucuronidation; therefore, LOPIMUNE has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.
HIV-1 Protease Inhibitor: amprenavir	↑ amprenavir ↓ lopinavir	LOPIMUNE should not be administered once-daily in combination with amprenavir (see DOSAGE AND ADMINISTRATION).
HIV-1 Protease Inhibitor: fosamprenavir / ritonavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse reactions has been observed with co-administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: indinavir	↑ indinavir	Decrease indinavir dose to 600 mg BID, when co-administered with lopinavir/ritonavir 400/100 mg BID (see PHARMACOLOGY). Lopinavir/ritonavir once-daily has not been studied in combination with indinavir.
HIV-1 Protease Inhibitor: nelfinavir	↑ nelfinavir ↑ M8 metabolite of nelfinavir ↓ lopinavir	LOPIMUNE should not be administered once-daily in combination with nelfinavir (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY).
HIV-1 Protease Inhibitor: ritonavir	↑ lopinavir	Appropriate doses of additional ritonavir in combination with lopinavir/ritonavir with respect to safety and efficacy have not been established.
HIV-1 Protease	↑ saquinavir	The saquinavir dose is 1000 mg BID, when co-administered with lopinavir/ritonavir 400/100 mg BID.

Inhibitor: saquinavir		Lopinavir /ritonavir once-daily has not been studied in combination with saquinavir.
HIV-1 Protease Inhibitor: tipranavir	↓ lopinavir AUC and C _{min}	LOPIMUNE should not be administered with tipranavir (500 mg twice-daily) co-administered with ritonavir (200 mg twice-daily).
HIV CCR5 – antagonist: Maraviroc	↑ maraviroc	Concurrent administration of maraviroc with lopinavir will increase plasma levels of maraviroc. When co-administered, patients should receive 150 mg BID of maraviroc. For further details see complete prescribing information for maraviroc.
Other Agents		
Antiarrhythmics : amiodarone, bepridil, lidocaine (systemic), and quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with LOPIMUNE .
Anticancer Agents: vincristine vinblastine nilotinib dasatinib	↑ anticancer agents	<p>Concentrations of vincristine or vinblastine may be increased when co-administered with lopinavir/ritonavir resulting in the potential for increased adverse events usually associated with these anticancer agents.</p> <p>For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when lopinavir/ritonavir is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as lopinavir/ritonavir. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.</p>
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized

		ratio) be monitored.
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Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ lopinavir ↓ phenytoin	<p>LOPIMUNE may be less effective due to decreased lopinavir plasma concentrations in patients taking decreased lopinavir plasma concentrations in patients taking these agents concomitantly.</p> <p>LOPIMUNE should not be administered once-daily in combination with carbamazepine, phenobarbital, or phenytoin.</p> <p>In addition, co-administration of phenytoin and lopinavir/ritonavir may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with LOPIMUNE.</p>
Antidepressant Bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Concurrent administration of bupropion with lopinavir may decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion). Patients receiving LOPIMUNE and bupropion concurrently should be monitored for an adequate for an adequate clinical response to bupropion.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and LOPIMUNE may increase concentrations of trazodone. Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	<p>For patients with renal impairment, the following dosage adjustments should be considered:</p> <ul style="list-style-type: none"> •For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. •For patients with $CL_{CR} < 30$ mL/min the dose of clarithromycin should be decreased by 75%. <p>No dose adjustment for patients with normal renal function is necessary.</p>

<p>Antifungals: ketoconazole, itraconazole, voriconazole</p>	<p>↑ketoconazole ↑ itraconazole ↓voriconazole</p>	<p>No dose adjustment for patients with normal renal function is necessary. High doses of ketoconazole (>200 mg/day) or itraconazole (> 200 mg/day) are not recommended. Co-administration of voriconazole with lopinavir/ritonavir has not been studied. However, a study has been shown that administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of lopinavir/ritonavir and voriconazole may result in decreased voriconazole concentrations and the potential for decreased voriconazole effectiveness and should be avoided, unless and assessment of the benefit/risk to the patient justifies the use of voriconazole. Otherwise, alternative antifungal therapies should be considered in these patients.</p>
<p>Anti-gout colchicine</p>	<p>↑ colchicine</p>	<p>Patients with renal or hepatic impairment should not be given colchicine with LOPIMUNE.</p> <p><u>Treatment of gout flares-co-administration of colchicine in patients on LOPIMUNE :</u> 0.6 mg (1tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.</p> <p><u>Prophylaxis of gout flares-co-administration of colchicine in patients on LOPIMUNE:</u> If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original colchicine regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.</p> <p><u>Treatment of familial Mediterranean fever (FMF)-coadministration of colchicine in patients on LOPIMUNE:</u> Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p>
<p>Antimycobacterial: rifabutin</p>	<p>↑ rifabutin and rifabutin metabolite</p>	<p>Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e. a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse reactions is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.</p>

Antimycobacterial: rifampin	↓ lopinavir	<p>May lead to loss of virologic response and possible resistance to lopinavir or to the class of protease inhibitors or other co-administered antiretroviral agents. A study evaluated combination of rifampin 600 mg QD, with lopinavir/ritonavir 800/200 mg twice daily or lopinavir/ritonavir 400/100 mg + ritonavir 300 mg twice daily. Pharmacokinetic and safety results from this study do not allow for a dose recommendation. Nine subjects (28%) experienced a ≥ grade 2 increase in ALT/AST, of which seven (21%) prematurely discontinued study per protocol. Based on the study design, it is not possible to determine whether the frequency or magnitude of the ALT/AST elevations observed is higher than what would be seen with rifampin alone.</p> <p>(see PHARMACOLOGY) for magnitude of interaction).</p>
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Benzodiazepines: parenterally administered midazolam	↑ midazolam	<p>Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, LOPIMUNE should not be given with orally administered midazolam (see CONTRAINDICATIONS). If lopinavir/ritonavir is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.</p>
Calcium Channel Blockers, dihydropyridine: e.g. felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: dexamethasone disulfiram/ metronidazole	↓ lopinavir	<p>Use with caution. Lopinavir may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.</p> <p>Lopinavir/ritonavir oral solution contains alcohol, which can produce disulfiram-like reactions when co administered with disulfiram or other drugs that produce this reaction (e.g. metronidazole)</p>

<p>Endothelin receptor antagonists: bosentan</p>	<p>↑ bosentan</p>	<p><u>Co-administration of bosentan in patients on LOPIMUNE:</u></p> <p>In patients who have been receiving LOPIMUNE for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p> <p><u>Co-administration of LOPIMUNE in patients on bosentan:</u></p> <p>Discontinue use of bosentan at least 36 hours prior to initiation of LOPIMUNE. After at least 10 days following the initiation of LOPIMUNE, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p>
<p>PDE5 inhibitors: sildenafil, tadalafil, vardenafil</p>	<p>↑ sildenafil ↑ tadalafil ↑ vardenafil</p>	<p>Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving LOPIMUNE. Co-administration of LOPIMUNE with these drugs is expected to substantially increase their concentrations and may result in an increase in associated adverse reactions including hypotension, syncope, visual changes and prolonged erection.</p> <p>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): Sildenafil is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) because a safe and effective dose has not been established when used with lopinavir/ritonavir (see Contraindications).</p> <p>The following dose adjustments are recommended for use of tadalafil with LOPIMUNE: <u>Co-administration of tadalafil in patients on LOPIMUNE:</u> In patients receiving LOPIMUNE for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Co-administration of LOPIMUNE in patients on tadalafil:</u> Avoid use of tadalafil during the initiation of LOPIMUNE. Stop tadalafil at least 24 hours prior to starting LOPIMUNE. After at least one week following the initiation of LOPIMUNE, resume tadalafil at 20 mg once daily. Increase to 40 mg once</p>

		<p>daily based upon individual tolerability.</p> <p>Use of PDE5 inhibitors for erectile dysfunction: It is recommended not to exceed the following doses:</p> <ul style="list-style-type: none"> • Sildenafil: 25 mg every 48 hours • Tadalafil: 10 mg every 72 hours • Vardenafil: 2.5 mg every 72 hours <p>Use with increased monitoring for adverse events.</p>
HMG-CoA Reductase Inhibitors: Atorvastatin rosuvastatin	<p>↑ atorvastatin</p> <p>↑ rosuvastatin</p>	<p>Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with LOPIMUNE.</p>
Immunosuppressants: cyclosporine, tacrolimus, rapamycin	<p>↑ immunosuppressants</p>	<p>Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with LOPIMUNE.</p>
Inhaled Steroid: fluticasone	<p>↑ fluticasone</p>	<p>Concomitant use of fluticasone propionate and lopinavir/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during post-marketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Co-administration of fluticasone propionate and lopinavir/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effect.</p>
Long-acting betaadrenoceptor agonist: salmeterol	<p>↑ salmeterol</p>	<p>Concurrent administration of salmeterol and LOPIMUNE is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.</p>

Narcotic Analgesic: methadone	↓ methadone	Dosage of methadone may need to be increased when coadministered with LOPIMUNE .
Contraceptive: ethinyl estradiol	↓ ethinyl estradiol	Because contraceptive steroid concentrations may be altered when LOPIMUNE is co-administered with oral contraceptives or with the contraceptive patch, alternative methods of non hormonal contraception are recommended

Drugs with No Observed or Predicted Interactions with lopinavir/ritonavir Drug interaction studies reveal no clinically significant interaction between lopinavir/ritonavir and desipramine (CYP2D6 probe), pravastatin, stavudine, lamivudine, omeprazole or ranitidine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between **LOPIMUNE** and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

Pregnancy

Pregnancy Category C

No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21) occurred.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily). There are, however, no adequate and well-controlled studies in pregnant women. **LOPIMUNE** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known

whether lopinavir is secreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving LOPIMUNE**.

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.

Hepatic impairment

LOPIMUNE is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased (see **WARNINGS AND PRECAUTIONS** and **PHARMACOLOGY**).

UNDESIRABLE EFFECTS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- PR Interval Prolongation, QT Interval Prolongation (see **WARNINGS AND PRECAUTIONS**)
- Drug Interactions (see **WARNINGS AND PRECAUTIONS**)
- Pancreatitis (see **WARNINGS AND PRECAUTIONS**)
- Hepatotoxicity (see **WARNINGS AND PRECAUTIONS**)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults: Clinical trial Experience

Treatment-Emergent Adverse Events

The safety profile of lopinavir/ritonavir in adults is primarily based on 1555 HIV-1 infected patients in clinical trials.

The most common adverse reaction was diarrhea, which was generally of mild to moderate severity. In study 730, the incidence of diarrhea of any severity during 48 weeks of therapy was 60% in patients receiving lopinavir/ritonavir tablets once daily compared to 57% in patients receiving lopinavir/ritonavir tablets twice daily. More patients receiving lopinavir/ritonavir tablets once daily (14, 4.2%) had ongoing diarrhea at the time of discontinuation as compared to patients receiving lopinavir/ritonavir tablets twice daily (6, 1.8%). In study 730, discontinuations due to any adverse reaction were 4.8% in patients receiving lopinavir/ritonavir tablets once daily as compared to 3% in patients receiving lopinavir/ritonavir tablets twice daily. In study 863, discontinuations of randomized therapy due to adverse reactions were 3.4% in lopinavir/ritonavir-treated and 3.7% in nelfinavir-treated patients.

Treatment-emergent clinical adverse reactions of moderate or severe intensity in $\geq 2\%$ of patients treated with combination therapy for up to 48 weeks (Study 863 and 730) and for up to 360 weeks (Study 720) are presented in Table 4 (treatment-naïve patients); and for up to 48 weeks (Study 888), 84 weeks (Study 957) and 144 weeks (Study 765) in Table 5 (protease inhibitor experienced patients).

Table 4: Percentage of Patients with Selected Treatment Emergent¹ Adverse Reactions of Moderate or Severe Intensity Reported in $\geq 2\%$ of Adult Antiretroviral Naive Patients.

	Study 863 (48 Weeks)		Study 720 360 Weeks)	Study 730 (48 Weeks)	
	Lopina vir/rito navir 400/10 0 mg Twice Daily + d4T + 3TC (N = 326)	Nelfinavir 750 mg Three Times Daily + d4T + 3TC (N = 327)	Lopinavi r/ritonavi r Twice Daily ² + d4T + 3TC (N =100)	Lopinavir/ Ritonavir 800/200 mg Once Daily + TDF +FTC (N=333)	Lopinavir/ ritonavir40 0/100 mg Twice Daily + TDF +FTC (N=331)
Endocrine Disorders					
Hypogonadism	0%	0%	2%	0%	0%
Gastrointestinal Disorders					
Diarrhea	16%	17%	28%	17%	15%
Nausea	7%	5%	16%	7%	5%
Vomiting	2%	2%	6%	3%	4%
Abdominal Pain	4%	3%	11%	1%	1%
Dyspepsia	2%	< 1%	6%	0%	0%
Flatulence	2%	1%	4%	1%	1%
General Disorders and Administration					
Site Conditions					
Asthenia	4%	3%	9%	< 1%	< 1%

Infections and Infestations					
Bronchitis	0%	0%	2%	0%	< 1%
Investigations					
Weight decreased	1%	< 1%	2%	0%	< 1%
Metabolism and Nutrition Disorders					
Anorexia	1%	< 1%	2%	< 1%	1%
Musculoskeletal and Connective Tissue Disorders					
Myalgia	1%	1%	2%	0%	0%
Nervous System Disorders					

Headache	2%	2%	6%	2%	2%
Paresthesia	1%	1%	2%	0%	0%
Psychiatric Disorders					
Insomnia	2%	1%	3%	1%	0%
Depression	1%	2%	0%	0%	0%
Libido decreased	< 1%	< 1%	2%	0%	< 1%
Skin and Subcutaneous Tissue Disorders					
Rash	1%	2%	5%	< 1%	1%
Vascular Disorders					
Vasodilation	0%	0%	3%	0%	0%

¹ Includes adverse reactions of possible or probable relationship to study drug.

² Includes adverse reaction data from dose group I (200/100 mg twice daily (N = 16) and 400/100 mg twice daily (N = 16)) and dose group II (400/100 mg twice daily (N = 35) and 400/200 mg twice daily (N = 33)). Within dosing groups, moderate to severe nausea of probable/possible relationship to lopinavir/ritonavir occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II. Definitions: d4T = Stavudine; 3TC = Lamivudine; TDF = Tenofovir Disoproxil Fumarate; FTC = Emtricitabine

Table 5: Percentage of Adult Patients with Selected Treatment Emergent¹ Adverse events of Moderate or Severe Intensity Reported in \geq 2% of Adult Protease Inhibitor-Experienced Patients

	Study 888 (48 weeks)		Study 957 ² and Study 765 ³ (84-144 Weeks)
	LPV/r 400/100 mg BID + NVP + NRTIs (n=148)	Investigators selected PIs + NVP + NRTIs (n=140)	LPV/r BID + NNRTI + NRTI (n=127)
Body as a Whole			
Abdominal Pain	2%	2%	4%
Asthenia	3%	6%	9%
Chills	2%	0%	0%
Fever	2%	1%	2%
Headache	2%	2%	3%
Cardiovascular			
Hypertension	0%	0%	2%
Digestive System			
Anorexia	1%	3%	0%
Diarrhoea	7%	9%	23%
Dyspepsia	1%	1%	2%
Dysphagia	2%	1%	0%
Flatulence	1%	2%	2%
Nausea	7%	16%	5%
Vomiting	4%	12%	2%
Metabolic and Nutritional			
Weight Loss	0%	1%	3%
Musculoskeletal			
Myalgia	1%	1%	2%
Nervous system			
Depression	1%	2%	2%
Insomnia	0%	2%	2%
Paraesthesia	1%	0%	2%
Skin and Appendages			
Rash	2%	1%	2%

¹ Includes adverse events of possible, probable, or unknown relationship to study drug

² Includes adverse event data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 84 weeks. Patients receiving LPV/r in combination with NRTIs and efavirenz.

³ Includes adverse event data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 144 weeks. Patients received LPV/r in combination with NRTIs and nevirapine.

Table 5: Percentage of Adult Patients with Selected treatment-emergent Adverse Reactions of Moderate or Severe intensity Reported in > 2% of adult Protease Inhibitor-Experienced Patients.

	Study 888(48 weeks)		Study 957 ² and study 765 ³ (84-144 weeks)
	LPV/r ² 400/100 mg Twice Daily +NVP+NRTIs(N=148)	Investigator-selected protease inhibitor(s) +NVP+NRTIs(N=140)	LPV/r ² twice daily+ NNRTI+NRTIs(N=127)
Gastrointestinal Disorders			
Diarrhea	7%	9%	23%
Nausea	7%	16%	5%
Vomiting	4%	12%	2%
Abdominal Pain	2%	2%	4%
Dyspepsia	1%	1%	2%
Flatulence	1%	2%	2%
Dysphasia	2%	1%	0%
General Disorders and Administration Site Conditions			
Asthenia	3%	6%	9%
Pyrexia	2%	1%	2%
Chills	2%	0%	0%
Investigations			

Weight decreased	0%	1%	3%
Metabolism and Nutrition Disorders			
Anorexia	1%	3%	0%
Musculoskeletal and Connective Tissue Disorders			
Myalgia	1%	1%	2%
Nervous System Disorders			
Headache	2%	3%	2%
Paresthesia	1%	0%	2%
Psychiatric Disorders			
Depression	1%	2%	2%
Insomnia	0%	2%	2%
Skin and Subcutaneous Tissue Disorders			
Rash	2%	1%	2%
Vascular Disorders			
Hypertension	0%	0%	2%
<p>¹ Includes adverse reactions of possible or probable relationship to study drug.</p> <p>² Includes adverse reaction data from patients receiving 400/100 mg twice daily (n = 29) or 533/133 mg twice daily (n = 28) for 84 weeks. Patients received lopinavir in combination with NRTIs and efavirenz.</p> <p>³ Includes adverse reaction data from patients receiving 400/100 mg twice daily (n = 36) or 400/200 mg twice daily (n = 34) for 144 weeks. Patients received lopinavir in combination with NRTIs and nevirapine.</p> <p>Definitions: NVP = Nevirapine; NRTI = Nucleoside Reverse Transcriptase Inhibitors; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitors</p>			

Less Common Adverse Reactions

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving lopinavir/ritonavir in the clinical trials supporting approval and of at moderate intensity are listed below by system organ class.

Blood and Lymphatic System Disorders

Anemia, leukopenia, lymphadenopathy, and splenomegaly

Cardiac Disorders

Atrial fibrillation, atrioventricular block, myocardial infarction, palpitation.

Ear and Labyrinth Disorders

Hyperacusis, tinnitus, and vertigo

Endocrine Disorders

Cushing's syndrome and hypothyroidism

Eye Disorders

Eye disorder and visual disturbance

Gastrointestinal Disorders

Abdominal distension, abdominal pain upper, constipation, dry mouth, enteritis, enterocolitis, enterocolitis hemorrhagic, eructation, esophagitis, fecal incontinence, gastric disorder, gastritis, gastroesophageal reflux disease, hemorrhoids, mouth ulceration, pancreatitis, periodontitis, stomach discomfort, and stomatitis

General Disorders and Administration Site Conditions

Chest pain, cyst, drug interaction, edema, edema peripheral, face edema, fatigue, hypertrophy, and malaise

Hepatobiliary Disorders

Cholangitis, cholecystitis, cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly, jaundice, and liver tenderness

Immune System Disorders

Drug hypersensitivity, hypersensitivity, and immune reconstitution syndrome

Infections and Infestations

Bacterial infection, cellulitis, folliculitis, furuncle, gastroenteritis, influenza, otitis media, perineal abscess, pharyngitis, rhinitis, sialoadenitis, sinusitis, and viral infection

Investigations

Drug level increased, glucose tolerance decreased, and weight increased

Metabolism and Nutrition Disorders

Decreased appetite, dehydration, diabetes mellitus, hypovitaminosis, increased appetite, lactic acidosis, lipomatosis, and obesity

Musculoskeletal and Connective Tissue Disorders

Arthralgia, arthropathy, back pain, muscular weakness, osteoarthritis, osteonecrosis, and pain in extremity

Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)

Benign neoplasm of skin, lipoma, and neoplasm

Nervous System Disorders

Ageusia, amnesia, ataxia, cerebral infarction, convulsion, dizziness, dysgeusia, dyskinesia, encephalopathy, extrapyramidal disorder, facial palsy, hypertonia, migraine, neuropathy, neuropathy peripheral, somnolence, and tremor

Psychiatric Disorders

Abnormal dreams, affect lability, agitation, anxiety, apathy, confusional state, nervousness, and thinking abnormal

Renal and Urinary Disorders

Nephritis, nephrolithiasis, renal disorder, and urine abnormality

Reproductive System and Breast Disorders

Breast enlargement, ejaculation disorder, erectile dysfunction, and gynecomastia

Respiratory, Thoracic and Mediastinal Disorders

Asthma, cough, dyspnea, and pulmonary edema

Skin and Subcutaneous Tissue Disorders

Acne, alopecia, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, dry skin, eczema, hyperhidrosis, idiopathic capillaritis, nail disorder, pruritis, rash generalized, rash maculo-papular, seborrhea, skin discoloration, skin hypertrophy, skin striae, skin ulcer, and swelling face

Vascular Disorders

Deep vein thrombosis, orthostatic hypotension, thrombophlebitis, varicose vein, and vasculitis

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in Table 6 (treatment naïve patients) and Table 7 (treatment experienced patients)

Table 6: Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Antiretroviral-Naïve Patients

		Study 863 (48 weeks)		Study 720(360 weeks)	Study 730 (48 weeks)	
Variable	Limit ¹	LPV/r 400/100 mg twice daily+ d4T + 3TC (N = 326)	Nelfin avir 750 mg three times daily+ d4T + 3TC (N = 327)	LPV/r twice daily+d4T +3TC(N=100)	LPV/r mg QD + TDF + FTC (N = 333)	LPV/r mg BID + TDF + FTC (N = 331)
Chemistry						
Glucose	High >250 mg/dl	2%	2%	4%	0%	<1%
Uric Acid	>12 mg/dl	2%	2%	5%	<1%	1%
SGOT/AST ²	>180 U/L	2%	4%	10%	1%	2%
SGPT/ALT ²	>215 U/L	4%	4%	11%	1%	1%
GGT	>300 U/L	N/A	N/A	10%	N/A	N/A
Total Cholesterol	>300 mg/dL	9%	5%	27%	4%	3%
Triglycerides	>750 mg/dL	9%	1%	29%	3%	6%
Amylase	>2 x ULN	3%	2%	4%	N/A	N/A
Lipase	>2 x ULN	N/A	N/A	N/A	3%	5%
Chemistry	Low					
Calculated	<50 mL/min	N/A	N/A	N/A	2%	2%
Creatinine clearance						
Hematology	Low					
Neutrophils	<0.75 x 10 ⁹ /L	1%	3%	5%	2%	1%

1 ULN = upper limit of the normal range; N/A = Not Applicable

2 Criterion for Study 730 was >5 x ULN (AST/ALT).

Table 7: Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Protease Inhibitor-Experienced Patients

		Study 888 (48 weeks)		Study 957 ² and Study 765 ³ (84-144 Weeks)
Variable	Limit ¹	LPV/r 400/100 mg BID + NVP + NRTIs (N=148)	Investigator-selected protease inhibitor(s) + NVP + NRTIs (N=140)	LPV/r 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	$0.75 \times 10^9/L$	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 LPV/r in combination with NRTIs and efavirenz. ³ Includes clinical laboratory data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 144 weeks. Patients received LPV/r in combination with NRTIs and nevirapine.				

Post-marketing Experience

The following adverse reactions have been reported during post-marketing use of Lopinavir/ritonavir. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to lopinavir/ritonavir exposure.

Body as a Whole: Redistribution/accumulation of body fat has been reported (see **WARNINGS AND PRECAUTIONS**).

Cardiovascular: Bradyarrhythmias.

Skin and Appendages: Stevens Johnson Syndrome and erythema multiforme.

OVERDOSAGE

Human experience of acute overdosage with **LOPIMUNE** is limited. Treatment of overdose with **LOPIMUNE** 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 **LOPIMUNE**. 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 **LOPIMUNE** is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

PACKAGING INFORMATION

LOPIMUNE Tablets..... Container of 60 tablets

Last updated: November 2010