For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Lopinavir and Ritonavir Tablets USP 200/50mg

LOPIMUNE

COMPOSITION
LOPIMUNE Tablets
Each film-coated tablet contains
Lopinavir USP ..... 200 mg
Ritonavir USP.....50 mg

COLOURS: Titanium Dioxide, Yellow Oxide of Iron, Red oxide of Iron

DOSAGE FORM
Film coated tablets

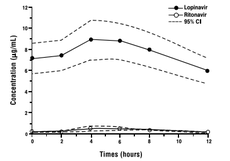
DESCRIPTION
LOPIMUNE is a co-formulation of lopinavir and ritonavir. As co-formulated in **LOPIMUNE**, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

PHARMACOLOGY
Pharmacodynamics
Lopinavir, an inhibitor of the HIV-1 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 and 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 EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of lopinavir and ritonavir is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after lopinavir and ritonavir 400/100 mg twice daily with food for 3 weeks from a pharmacokinetic study in HIV-1 infected adult subjects (n = 19).

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



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Absorption
In a pharmacokinetic study in HIV-1 positive subjects (n = 19), multiple dosing with 400/100 mg lopinavir and ritonavir twice daily with food for 3 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 µg/mL and minimum concentration within a dosing interval was 5.5 ± 2.7 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 µg●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 200/50mg lopinavir and ritonavir tablets are similar to three 133.3/33.3 mg lopinavir and ritonavir capsules under fed conditions with less pharmacokinetic variability.

Effects of Food on Oral Absorption
Lopinavir and ritonavir Tablets
No clinically significant changes in C_{max} and AUC were observed following administration of lopinavir and ritonavir tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of lopinavir and ritonavir tablets with a moderate fat meal (500 to 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 and ritonavir tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9% but not C_{max}. Therefore, lopinavir and 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 and 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 ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg lopinavir and 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.

Elimination
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 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 and ritonavir have been evaluated in HIV-1 infected subjects naive to antiretroviral treatment. Lopinavir and 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 and 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 ± 1.6 µg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 154.1 ± 61.4 µg•h/mL.

The pharmacokinetics of once daily lopinavir and ritonavir has also been evaluated in treatment experienced HIV-1 infected subjects. Lopinavir exposure (C_{max}, AUC_{0-24hr}, $C_{min,ss}$) with once daily lopinavir and 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) msec-onds (msec) for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily lopinavir and ritonavir, respectively. Lopinavir and 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 and ritonavir doses at steady state.

PR interval prolongation was also noted in subjects receiving lopinavir and 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 and ritonavir, respectively (see **WARNINGS AND PRECAUTIONS**).

Special Populations
Gender, Race and Age
No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified. Lopinavir pharmacokinetics have not been studied in elderly patients.

Pediatric Patients
Lopinavir and ritonavir once daily has not been evaluated in pediatric patients.

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

Hepatic Impairment
Lopinavir is principally metabolized and eliminated by the liver. Multiple dosing of lopinavir and ritonavir 400/100 mg twice daily to HIV-1 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-1 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 lopinavir and ritonavir to subjects with hepatic impairment. Lopinavir and ritonavir has not been studied in patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

INDICATIONS
Lopinavir and ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients.

The following points should be considered when initiating therapy with lopinavir and ritonavir:
- The use of other active agents with lopinavir and ritonavir is associated with a greater likelihood of treatment response.
- Genotypic or phenotypic testing and/or treatment history should guide the use of lopinavir and ritonavir. The number of baseline lopinavir resistance-associated substitutions affects the virologic response to lopinavir and ritonavir.

DOSAGE AND ADMINISTRATION
Lopinavir and ritonavir tablets may be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

Adult Patients
- Lopinavir and ritonavir tablets 400/100 mg (given as two 200/50 mg tablets) twice daily.
- Lopinavir and 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 lopinavir and ritonavir 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.

Lopinavir and ritonavir should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin (see **WARNINGS AND PRECAUTIONS – Drug Interactions**).

Concomitant Therapy: Efavirenz, Nevirapine, or Nelfinavir
(see **WARNINGS AND PRECAUTIONS – Drug Interactions**)

Lopinavir and ritonavir tablets should not be administered as a once daily regimen in combination with efavirenz, nevirapine, or nelfinavir.
- A dose increase is recommended for all patients who use lopinavir and ritonavir tablets. The recommended dose of lopinavir and ritonavir tablets is 500/125 mg (such as two 200/50 tablets and one 100/25 mg tablet) twice daily in combination with efavirenz, nevirapine, or nelfinavir.

Pediatric Patients
Lopinavir and ritonavir tablets should not be administered once daily in pediatric patients < 18 years of age.

Special attention should be given to accurate calculation of the dose of lopinavir and ritonavir, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors, and overdose.

Prescribers should calculate the appropriate dose of lopinavir and ritonavir for each individual child based on body weight (kg) or body surface area (BSA) to avoid underdosing or exceeding the recommended adult dose.

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

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

The lopinavir and ritonavir 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 (m^2) × Prescribed lopinavir dose (mg/m^2) = Administered lopinavir dose (mg)

Before prescribing lopinavir and ritonavir tablets, children should be assessed for the ability to swallow intact tablets. If a child is unable to reliably swallow a lopinavir and ritonavir tablet, the lopinavir and ritonavir oral solution formulation should be prescribed.

6 Months to 18 Years:
Without Concomitant Efavirenz, Nevirapine, or Nelfinavir

Dosing recommendations using tablets
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 lopinavir and ritonavir tablets.

Table 1. Pediatric Dosing Recommendations for Patients 6 Months to 18 Years of Age Based on Body Weight or Body Surface Area for Lopinavir and ritonavir Tablets Without Concomitant Efavirenz, Nevirapine, 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 and ritonavir oral solution is available for children with BSA less than 0.6m^2 or those who are unable to reliably swallow a tablet.

Concomitant Therapy: Efavirenz, Nevirapine, or Nelfinavir

Dosing recommendations using tablets
Table 2 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on body weight or body surface area for lopinavir and ritonavir tablets when given in combination with efavirenz, nevirapine, or nelfinavir.

Table 2. Pediatric Dosing Recommendations for Patients 6 Months to 18 Years of Age Based on Body Weight or Body Surface Area for Lopinavir and ritonavir Tablets With Concomitant Efavirenz, Nevirapine, or Nelfinavir†

Body Weight (kg)	Body Surface Area (m^2)*	Recommended number of 100/25 mg Tablets Twice-Daily
15 to 20	≥ 0.6 to < 0.8	2
>20 to 30	≥ 0.8 to < 1.2	3
>30 to 45	≥ 1.2 to <1.7	4 (or two 200/50 mg tablets)
>45	≥1.7	5

* Lopinavir and ritonavir oral solution is available for children with a BSA less than 0.6m^2 or those who are unable to reliably swallow a tablet.
† Please refer to the individual product labels for appropriate dosing in children.

CONTRAINDICATIONS
- Lopinavir and ritonavir is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) to any of its ingredients, including ritonavir.
- Co-administration of lopinavir and ritonavir 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 lopinavir and ritonavir 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 3.

Table 3. Drugs That are Contraindicated with Lopinavir and ritonavir

Drug Class	Drugs Within Class That are Contraindicated with Lopinavir and ritonavir	Clinical Comments
Alpha 1- Adrenoreceptor Antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can results in hypotension.
Antimycobacterial	Rifampin	May lead to loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors or other co-administered antiretroviral agents (see **WARNINGS AND PRECAUTIONS – Drug Interactions**).
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	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 John's Wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
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 and ritonavir. There is an increased potential for sildenfil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope (see **WARNINGS AND PRECAUTIONS – Drug Interactions**).
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/Hypnotics	Triazolam; orally administered midazolam[b]	Prolonged or increased sedation or respiratory depression.

[a] see **WARNINGS AND PRECAUTIONS – Drug Interactions**, Table 4 for co-administration of sildenafil in patient with erectile dysfunction.
[b] see **WARNINGS AND PRECAUTIONS – Drug Interactions**, Table 4 for parenterally administered midazolam.

WARNINGS AND PRECAUTIONS
Drug Interactions
CYP3A Enzyme Inhibition
See Tables 3 and 4 for listing of drugs that are contraindicated for use with lopinavir and ritonavir due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity (see **CONTRAINDICATIONS**).

Potential for Lopinavir and ritonavir 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 lopinavir and ritonavir 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 4.

Additionally, lopinavir and ritonavir 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 lopinavir and ritonavir's therapeutic effect. Although not observed in the lopinavir and ritonavir/ketoconazole drug interaction study, co-administration of lopinavir and ritonavir and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Established and Other Potentially Significant Drug Interactions
Table 4 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 4. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comments
HIV-1 Antiviral Agents		
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 twice daily, when co-administered with lopinavir and ritonavir 400/100 mg twice daily. Lopinavir and ritonavir once daily has not been studied in combination with indinavir.
HIV-1 Protease Inhibitor: nelfinavir	↑ nelfinavir ↑ M8 metabolite of nelfinavir ↓ lopinavir	Lopinavir and ritonavir should not be administered once daily in combination with nelfinavir (see **DOSAGE AND ADMINISTRATION**).
HIV-1 Protease Inhibitor: ritonavir	↑ lopinavir	Appropriate doses of additional ritonavir in combination with lopinavir and ritonavir with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: saquinavir	↑ saquinavir	The saquinavir dose is 1000 mg twice daily, when co-administered with lopinavir and ritonavir 400/100 mg twice daily. Lopinavir and ritonavir once daily has not been studied in combination with saquinavir.
HIV-1 Protease Inhibitor: tipranavir	↓ lopinavir AUC and C_{min}	Lopinavir and ritonavir 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 and ritonavir will increase plasma levels of maraviroc. When co-administered, patients should receive 150 mg twice daily of maraviroc. For further details see complete prescribing information for maraviroc.
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz nevirapine	↓ lopinavir	Lopinavir and ritonavir dose increase is recommended in all patients (see **DOSAGE AND ADMINISTRATION**). Increasing the dose of lopinavir and 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 and ritonavir tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz. Increasing the dose of lopinavir and 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 and ritonavir tablets 400/100 mg twice daily without efavirenz. Lopinavir and ritonavir should not be administered once daily in combination with efavirenz or nevirapine (see **DOSAGE AND ADMINISTRATION**).
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		Lopinavir and ritonavir tablets can be administered simultaneously with didanosine without food.
Nucleoside Reverse Transcriptase Inhibitor: tenofovir	↑ tenofovir	Lopinavir and ritonavir increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir and ritonavir and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside Reverse Transcriptase Inhibitor: abacavir zidovudine	↓ abacavir ↓ zidovudine	Lopinavir and ritonavir induces glucuronidation; therefore, lopinavir and ritonavir has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.
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 lopinavir and ritonavir.
Anticancer Agents: vincristine, vinblastine, dasatinib, nilotinib	↑ anticancer agents	Concentrations of these drugs may be increased when co-administered with lopinavir and ritonavir resulting in the potential for increased adverse events usually associated with these anticancer agents. 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 and 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 and ritonavir. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.
Anticoagulant: warfarin, rivaroxaban	↑ rivaroxaban	Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored. Avoid concomitant use of rivaroxaban and lopinavir and ritonavir. Coadministration of lopinavir and ritonavir and rivaroxaban is expected to result in increased exposure of rivaroxaban which may lead to risk of increased bleeding.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ lopinavir ↓ phenytoin	Lopinavir and ritonavir may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly and should be used with caution. Lopinavir and ritonavir should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin. In addition, co-administration of phenytoin and lopinavir and ritonavir may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with lopinavir and ritonavir.
Anticonvulsants: lamotrigine, valproate	↓ lamotrigine ↓ or ↔ valproate	Co-administration of lopinavir and ritonavir and lamotrigine or valproate may decrease the exposure of lamotrigine or valproate. A dose increase of lamotrigine or valproate may be needed when co-administered with lopinavir and ritonavir and therapeutic concentration monitoring for lamotrigine may be indicated; particularly during dosage adjustments.
Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Concurrent administration of bupropion with lopinavir and ritonavir may decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion). Patients receiving lopinavir and ritonavir and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and lopinavir and ritonavir 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	For patients with renal impairment, the following dosage adjustments should be considered: • 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%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole (>200 mg/day) or itraconazole (>200 mg/day) are not recommended. Co-administration of voriconazole with lopinavir and 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 and ritonavir and voriconazole may result in decreased voriconazole concentrations and the potential for decreased voriconazole effectiveness and should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Otherwise, alternative antifungal therapies should be considered in these patients.
Anti-gout: colchicine	↑ colchicine	Patients with renal or hepatic impairment should not be given colchicine with lopinavir and ritonavir. Treatment of gout flares-co-administration of colchicine in patients on lopinavir and ritonavir: 0.6mg (1 tablet) x 1 dose, followed by 0.3mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. Prophylaxis of gout flares-co-administration of colchicine in patients on lopinavir and ritonavir: If the original colchicine regimen was 0.6mg twice a day, the regimen should be adjusted to 0.3mg once a day. If the original colchicine regimen was 0.6mg once a day, the regimen should be adjusted to 0.3mg once every other day. Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on lopinavir and ritonavir. Maximum daily dose of 0.6mg (may be given as 0.3mg twice a day).
Antimycobacterial: rifabutin	↑ rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300mg/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.
Antimycobacterial: rifampin	↓ lopinavir	May lead to loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors or other co-administered antiretroviral agents. A study evaluated combination of rifampin 600 mg once daily with lopinavir and ritonavir 800/200 mg twice daily or lopinavir and 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.
Antiparasitic: atovaquone	↓atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Benzodiazepines: parenterally administered midazolam	↑ midazolam	Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, lopinavir and ritonavir should not be given with orally administered midazolam (see **CONTRAINDICATIONS**). If lopinavir and ritonavir is co-administered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
Contraceptive: ethinyl estradiol	↓ ethinyl estradiol	Because contraceptive steroid concentrations may be altered when lopinavir and ritonavir is co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.
Corticosteroids (systemic): e.g. budesonide, dexamethasone, prednisone	↓ lopinavir ↑ glucocorticoids	Use with caution. Lopinavir and ritonavir may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly. Concomitant use may result in increased steroid concentrations and reduced serum cortisol concentrations. Concomitant use of glucocorticoids that are metabolized by CYP3A, particularly for long-term use, should consider the potential benefit of treatment versus the risk of systemic corticosteroid effects. Concomitant use may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.
Dihydropyridine Calcium Channel Blockers: e.g. felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Endothelin Receptor Antagonists: bosentan	↓ bosentan	Co-administration of bosentan in patients on lopinavir and ritonavir: In patients who have been receiving lopinavir and ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Co-administration of lopinavir and ritonavir in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of lopinavir and ritonavir. After at least 10 days following the initiation of lopinavir and ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
HCV-Protease Inhibitor: boceprevir	↓ lopinavir ↓ boceprevir ↓ ritonavir	It is not recommended to co-administer lopinavir and ritonavir and boceprevir. Concomitant administration of lopinavir and ritonavir and boceprevir reduced boceprevir, lopinavir and ritonavir steady-state exposures.
HCV-Protease Inhibitor: telaprevir	↓ telaprevir ↔ lopinavir	It is not recommended to co-administer lopinavir and ritonavir and telaprevir. Concomitant administration of lopinavir and ritonavir and telaprevir reduced steady-state telaprevir exposure, while the steady-state lopinavir exposure was not affected.
HMG-CoA Reductase Inhibitors: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. See Drugs with No Observed or Predicted Interactions with lopinavir and ritonavir for drug interaction data with other HMG-CoA reductase inhibitors.
Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus	↑immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir.
Inhaled or Intranasal Steroids e.g.: fluticasone, budesonide	↑ glucocorticoids	Concomitant use of lopinavir and ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use may result in increased steroid concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients when certain ritonavircontaining products have been co-administered with fluticasone propionate or budesonide.
Long-acting beta-adrenoceptor Agonist: salmeterol	↑ salmeterol	Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Narcotic Analgesic: methadone fentanyl	↓ methadone ↑ fentanyl	Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. Concentrations of fentanyl are expected to increase. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with lopinavir and ritonavir.

PDE5 inhibitors: avanafil, sildenafil, tadalafil, vardenafil	↑ avanafil ↑ sildenafil ↑ tadalafil ↑ vardenafil	Do not use lopinavir and ritonavir with avanafil because a safe and effective avanafil dosage regimen has not been established. Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving lopinavir and ritonavir. Co-administration of lopinavir and ritonavir with these drugs is expected to substantially increase their concentrations and may result in an increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection. 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 and ritonavir (see **CONTRAINDICATIONS**). The following dose adjustments are recommended for use of tadalafil with lopinavir and ritonavir: Co-administration of tadalafil in patients on lopinavir and ritonavir: In patients receiving lopinavir and ritonavir for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Co-administration of lopinavir and ritonavir in patients on tadalafil: Avoid use of tadalafil during the initiation of lopinavir and ritonavir. Stop tadalafil at least 24 hours prior to starting lopinavir and ritonavir. After at least one week following the initiation of lopinavir and ritonavir, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE5 inhibitors for erectile dysfunction: It is recommended not to exceed the following doses: • Sildenafil: 25 mg every 48 hours • Tadalafil: 10 mg every 72 hours • Vardenafil: 2.5 mg every 72 hour Use with increased monitoring for adverse events.

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

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

Pancreatitis
Pancreatitis has been observed in patients receiving lopinavir and ritonavir therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to lopinavir and 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 lopinavir and ritonavir 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 lopinavir and ritonavir and/or other antiretroviral therapy should be suspended as clinically appropriate.

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 lopinavir and ritonavir.

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 and 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 and ritonavir in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with lopinavir and ritonavir therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with lopinavir and ritonavir 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 lopinavir and ritonavir treatment.

QT Interval Prolongation
Postmarketing cases of QT interval prolongation and torsade de pointes have been reported although causality of lopinavir and 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.

PR Interval Prolongation
Lopinavir/ritonavir prolongs the PR interval in some patients. Cases of second or third degree atrioventricular block have been reported. Lopinavir and ritonavir should be used with caution in patients with underlying structural heart disease, pre-existing 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 and 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 lopinavir and ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is 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-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.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lopinavir and 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 jirovecii* pneumonia [PCP], 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.

Lipid Elevations
Treatment with lopinavir and 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 lopinavir and ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with lopinavir and ritonavir and HMG-CoA reductase inhibitors (see **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS – Drug Interactions**).

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.

Patients with Hemophila
Increased bleeding, including spontaneous skin hematomas and hemarthrosis have been reported 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.

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

Pregnancy
Pregnancy Category C.

Human Data:
There are no adequate and well-controlled studies in pregnant women. Lopinavir and ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data:
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).

Lactation
The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed 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 breastfeed if they are receiving lopinavir and ritonavir.

Geriatric Use
Clinical studies of lopinavir and 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 and 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
Lopinavir and ritonavir 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.

UNDESIRABLE EFFECTS
The following are the adverse reactions
- QT Interval Prolongation, PR 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 reactions 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 clinical practice.

Adult Clinical Trial Experience
The safety profile of lopinavir and ritonavir in adults is primarily based on 1964 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 and ritonavir tablets once daily compared to 57% in patients receiving lopinavir and ritonavir tablets twice daily. More patients receiving lopinavir and ritonavir tablets once daily (14, 4.2%) had ongoing diarrhea at the time of discontinuation as compared to patients receiving lopinavir and ritonavir tablets twice daily (6, 1.8%). In study 730, discontinuations due to any adverse reaction were 4.8% in patients receiving lopinavir and ritonavir tablets once daily as compared to 3% in patients receiving lopinavir and ritonavir tablets twice daily. In study 802, the incidence of diarrhea of any severity during 48 weeks of therapy was 50% in patients receiving lopinavir and ritonavir tablets once daily compared to 39% in patients receiving lopinavir and ritonavir tablets twice daily. Moderate or severe drug-related diarrhea occurred in 14% of patients receiving lopinavir and ritonavir tablets once daily as compared to 11% in patients receiving lopinavir and ritonavir tablets twice daily. At the time of discontinuation, 19 (6.3%) patients receiving lopinavir and ritonavir tablets once daily had ongoing diarrhea, as compared to 11 (3.7%) patients receiving lopinavir and ritonavir tablets twice daily. Discontinuations due to any adverse reaction occurred in 4.3% of patients receiving lopinavir and ritonavir tablets once daily compared to 7.0% in patients receiving lopinavir and ritonavir tablets twice daily. In study 863, discontinuations of symptomized therapy due to adverse reactions were 3.4% in lopinavir and ritonavir-treated and 3.7% in nelfinavir-treated patients.

Treatment-emergent clinical adverse reactions of moderate or severe intensity in ≥ 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 5 (treatment-naïve patients) and for up to 48 weeks (Study 888 and 802), 84 weeks (Study 957) and 144 weeks (Study 765) in Table 6 (protease inhibitor-experienced patients).

Table 5. Percentage of Adult Patients with Selected Treatment-Emergent[1] Adverse Reactions of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naive Patients

	Study 863 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
	Lopinavir and ritonavir 400/100 mg Twice Daily + d4T + 3TC (N = 326)	Nelfinavir 750 mg Three Times Daily + d4T + 3TC (N = 327)	Lopinavir and ritonavir Twice Daily[2] + d4T + 3TC (N = 100)	Lopinavir and ritonavir 800/200 mg Once Daily + TDF +FTC (N=333)	Lopinavir and ritonavir 400/100 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 and 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 6. Percentage of Adult Patients with Selected Treatment-Emergent[1] 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)	Study 802 (48 Weeks)	
	Lopinavir and ritonavir 400/100 mg Twice Daily + NVP + NRTIs (N = 148)	Investigator-Selected Protease Inhibitor(s) + NVP + NRTIs (N = 140)	Lopinavir and ritonavir Twice Daily + NNRTI + NRTIs (N = 127)	Lopinavir and ritonavir 800/200mg Once Daily + NRTIs (N = 300)	Lopinavir and ritonavir 400/100mg Twice Daily + NRTIs (N = 299)
Gastrointestinal Disorders					
Diarrhea	7%	9%	23%	14%	11%
Nausea	7%	16%	5%	3%	7%
Vomiting	4%	12%	2%	2%	3%
Abdominal Pain	2%	2%	4%	2%	<1%
Abdominal Pain Upper	N/A	N/A	N/A	1%	2%
Dyspepsia	1%	1%	2%	1%	<1%
Flatulence	1%	2%	2%	1%	1%
Dysphasia	2%	1%	0%	0%	0%
General Disorders and Administration Site Conditions					
Asthenia	3%	6%	9%	<1%	<1%
Pyrexia	2%	1%	2%	0%	<1%
Chills	2%	0%	0%	0%	0%
Investigations					
Weight decreased	0%	1%	3%	<1%	<1%
Metabolism and Nutrition Disorders					
Anorexia	1%	3%	0%	0%	1%
Musculoskeletal and Connective Tissue Disorders					
Myalgia	1%	1%	2%	0%	0%
Nervous System Disorders					
Headache	2%	3%	2%	<1%	0%
Paresthesia	0%	1%	2%	0%	0%
Psychiatric Disorders					
Depression	1%	2%	3%	<1%	0%
Insomnia	0%	2%	2%	0%	<1%
Skin and Subcutaneous Tissue Disorders					
Rash	2%	1%	2%	0%	0%
Vascular Disorders					
Hypertension	0%	0%	2%	0%	0%

1 Includes adverse reactions of possible or probable relationship to study drug.
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 and ritonavir in combination with NRTIs and efavirenz.
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 and ritonavir in combination with NRTIs and nevirapine.
Definitions: NVP = Nevirapine; NRTI = Nucleoside Reverse Transcriptase Inhibitors; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitors

Less Common Adverse Reactions
Treatment-emergent adverse reactions occurrng in less than 2% of adult patients receiving lopinavir and ritonavir in the clinical trials supporting approval and of at least moderate intensity are listed below by system organ class.

Blood and Lymphatic System Disorders
Anemia, leukopenia, lymphadenopathy, neutropenia, and splenomegaly.

Cardiac Disorders
Angina pectoris, atrial fibrillation, atrioventricular block, myocardial infarction, palpitation, and tricuspid valve incompetence.

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 discomfort, abdominal distension, abdominal pain lower, constipation, duodenitis, dry mouth, enteritis, enterocolitis, enterocolitis hemorrhagic, eructation, esophagitis, fecal incontinence, gastric disorder, gastric ulcer, gastritis, gastroesophageal reflux disease, hemorrhoids, mouth ulceration, pancreatitis, periodontitis, rectal hemorrhage, 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, bronchopneumonia, 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, balance disorder, 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, disorientation, mood swings, nervousness, and thinking abnormal.

Renal and Urinary Disorders
Hematuria, nephritis, nephrolithiasis, renal disorder, urine abnormality and urine odor abnormal.

Reproductive System and Breast Disorders
Breast enlargement, ejaculation disorder, erectile dysfunction, gynecomastia and menorrhagia.

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 7 (treatment-naive patients) and Table 8 (treatment-experienced patients).

Table 7. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-Naive Patients

Variable	Limit[1]	Study 863 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
		Lopinavir and ritonavir 400/100 mg Twice Daily + d4T +3TC (N = 326)	Nelfinavir 750 mg Three Times Daily + d4T +3TC (N = 327)	Lopinavir and ritonavir Twice Daily + d4T + 3TC (N = 100)	Lopinavir and ritonavir Once Daily + TDF +FTC (N=333)	Lopinavir and ritonavir Twice Daily + TDF +FTC (N=331)
Chemistry	**High**					
Glucose	> 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 Creatinine Clearance	< 50 mL/min	N/A	N/A	N/A	2%	2%
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 >5x ULN (AST/ALT).

Table 8. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

Variable	Limit[1]	Study 888 (48 Weeks)		Study 957[2] and Study 765[3] (84-144 Weeks)	Study 802 (48 Weeks)	
		Lopinavir and ritonavir 400/100 mg Twice Daily + NVP +NRTIs (N = 148)	Investigator-Selected Protease Inhibitor(s) + NVP + NRTIs (N = 140)	Lopinavir and ritonavir Twice Daily + NNRTI + NRTIs (N = 127)	Lopinavir and ritonavir 800/200 mg Once Daily +NRTIs (N = 300)	Lopinavir and ritonavir 400/100 mg Twice Daily + NRTIs (N = 299)
Chemistry	**High**					
Glucose	>250 mg/dL	1%	2%	5%	2%	2%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%	1%	1%
SGOT/AST[4]	>180 U/L	5%	11%	8%	3%	2%
SGPT/ALT[4]	>215 U/L	6%	13%	10%	2%	2%
GGT	>300 U/L	N/A	N/A	29%	N/A	N/A
Total Cholesterol	>300 mg/dL	20%	21%	39%	6%	7%
Triglycerides	>750 mg/dL	25%	21%	36%	5%	6%
Amylase	>2 x ULN	4%	8%	8%	4%	4%
Lipase	>2 x ULN	N/A	N/A	N/A	4%	1%
Creatine Phosphokinase	>4 x ULN	N/A	N/A	N/A	4%	5%
Chemistry	**Low**					
Calculated Creatinine Clearance	<50mL/min	N/A	N/A	N/A	3%	3%
Inorganic Phosphorus	<1.5 mg/dL	1%	0%	2%	1%	<1%
Hematology	**Low**					
Neutrophils	<0.75 x 10^9/L	1%	2%	4%	3%	4%
Hemoglobin	<80g/L	1%	1%	1%	1%	2%

1 ULN = upper limit of the normal range; N/A = Not Applicable.
2 Includes clinical laboratory 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 and ritonavir in combination with NRTIs and efavirenz.
3 Includes clinical laboratory 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 and ritonavir in combination with NRTIs and nevirapine.
4 Criterion for Study 802 was > 5 x ULN (AST/ALT).

Pediatric Clinical Trial Experience
Lopinavir and ritonavir oral solution dosed up to 300/75 mg/m^2 has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse reaction profile seen during Study 940 was similar to that for adult patients.

Dysgeusia (22%), vomiting (21%), and diarrhea (12%) were the most common adverse reactions of any severity reported in pediatric patients treated with combination therapy for up to 48 weeks in Study 940. A total of 8 patients experienced adverse reactions of moderate to severe intensity. The adverse reactions meeting these criteria and reported for the 8 subjects include: hypersensitivity (characterized by fever, rash and jaundice), pyrexia, viral infection, constipation, hepatomegaly, pancreatitis, vomiting, alanine aminotransferase increased, dry skin, rash, and dysgeusia. Rash was the only event of those listed that occurred in 2 or more subjects (N = 3).

Lopinavir and ritonavir oral solution dosed at 300/75 mg/m^2 has been studied in 31 pediatric patients 14 days to 6 months of age. The adverse reaction profile in Study 1030 was similar to that observed in older children and adults. No adverse reaction was reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included decreased neutrophil count (N=3), anemia (N=2), high potassium (N=2), and low sodium (N=2).

Lopinavir and ritonavir oral solution and soft gelatin capsules dosed at higher than recommended doses including 400/100 mg/m^2 (without concomitant NNRTI) and 480/120 mg/m^2 (with concomitant NNRTI) have been studied in 26 pediatric patients 7 to 18 years of age in Study 1038. Patients also had saquinavir mesylate added to their regimen at Week 4. Rash (12%), blood cholesterol abnormal (12%) and blood triglycerides abnormal (12%) were the only adverse reactions reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included rash (N=3), blood triglycerides abnormal (N=3), and electrocardiogram QT prolonged (N=2). Both subjects with QT prolongation had additional predisposing conditions such as electrolyte abnormalities, concomitant medications, or pre-existing cardiac abnormalities.

Laboratory Abnormalities
The percentages of pediatric patients treated with combination therapy including lopinavir and ritonavir with Grade 3-4 laboratory abnormalities are presented in Table 9.

Table 9. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients in Study 940

Variable	Limit[1]	Lopinavir and ritonavir Twice Daily + RTIs (N = 100)
Chemistry	**High**	
Sodium	> 149 mEq/L	3%
Total Bilirubin	≥ 3.0 x ULN	3%
SGOT/AST	> 180 U/L	8%
SGPT/ALT	> 215 U/L	7%
Total Cholesterol	> 300 mg/dL	3%
Amylase	> 2.5 x ULN	7%[2]
Chemistry	**Low**	
Sodium	< 130 mEq/L	3%
Hematology	**Low**	
Platelet Count	< 50 x 10^9/L	4%
Neutrophils	< 0.40 x 10^9/L	2%

1 ULN = upper limit of the normal range.
2 Subjects with Grade 3-4 amylase confirmed by elevations in pancreatic amylase.

Postmarketing Experience
The following adverse reactions have been reported during postmarketing use of lopinavir and 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 and ritonavir exposure.

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

Cardiovascular
Bradyarrhythmias. First–degree AV block, second-degree AV block, third-degree AV block, QTc interval prolongation, torsades (torsade) de pointes (see **WARNINGS AND PRECAUTIONS**).

Skin and Appendages
Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and erythema multiforme.

OVERDOSAGE
Human experience of acute overdosage with lopinavir and ritonavir is limited. Treatment of overdose with lopinavir and 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 and ritonavir. If indicated, elimination of unabsorbed drug should be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since lopinavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

SHELF-LIFE
24 Months

INCOMPATIBILITIES
NA

STORAGE AND HANDLING INSTRUCTIONS
Store at 20°C to 25° C (68°F to 77°F)

PACKAGING INFORMATION:
LOPIMUNE Tablets Container of 60's

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