

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LOPINAVIR AND RITONAVIR ORAL SOLUTION safely and effectively. See full prescribing information for LOPINAVIR AND RITONAVIR ORAL SOLUTION.

**LOPINAVIR AND RITONAVIR solution, for oral use**  
**Initial U.S. Approval: 2000**

### RECENT MAJOR CHANGES

Contraindications (4)	11/2016
Warnings and Precautions	11/2016
Diabetes and Mellitus/Hyperglycemia (5.7)	

### INDICATIONS AND USAGE

Lopinavir and ritonavir is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older). (1)

### DOSAGE AND ADMINISTRATION

Oral solution: must be taken with food. (2.1)

#### Adults (2.2):

- Total recommended daily dosage is 800/200 mg given once or twice daily.
- Lopinavir and ritonavir can be given as once daily or twice daily regimen. See Full Prescribing Information for details.
- Lopinavir and ritonavir once daily dosing regimen is not recommended in:
  - 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. (12.4)
  - In combination with carbamazepine, phenobarbital, or phenytoin. (7.3)
  - In combination with efavirenz, nevirapine, or nelfinavir. (12.3)
  - In pregnant women. (2.4, 8.1, 12.3)

#### Pediatric Patients (14 days and older) (2.3):

- Lopinavir and ritonavir once daily dosing regimen is not recommended in pediatric patients.

- Twice daily dose is based on body weight or body surface area.

#### Concomitant Therapy in Adults and Pediatric Patients:

- Dose adjustments of lopinavir and ritonavir may be needed when co-administering with efavirenz, nevirapine, or nelfinavir. (2.2, 2.3, 7.3)
- Lopinavir and ritonavir oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained (2.3, 5.2)

#### Pregnancy (2.4):

- 400/100 mg twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions.
- There are insufficient data to recommend a lopinavir and ritonavir dose for pregnant patients with any documented lopinavir and ritonavir-associated resistance substitutions.
- No dose adjustment of lopinavir and ritonavir is required for patients during the postpartum period.

### DOSAGE FORMS AND STRENGTHS

- Oral solution: 80 mg lopinavir and 20 mg ritonavir per milliliter (3)

### CONTRAINDICATIONS

- Hypersensitivity to lopinavir and ritonavir (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme,

urticaria, angioedema) or any of its ingredients, including ritonavir. (4)

- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated plasma levels may result in serious and/or life-threatening events. (4)
- Co-administration 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. (4)

### WARNINGS AND PRECAUTIONS

The following have been observed in patients receiving lopinavir and ritonavir:

- The concomitant use of lopinavir and ritonavir and certain other drugs may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7.3)
- Toxicity in preterm neonates: Lopinavir and ritonavir oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of lopinavir and ritonavir oral solution in this patient population has not been established. (2.3, 5.2).
- Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate. (5.3)
- Hepatotoxicity: Fatalities have occurred. Monitor liver function before and during therapy, especially in patients with underlying hepatic disease, including hepatitis B and hepatitis C, or marked transaminase elevations. (5.4, 8.6)
- QT interval prolongation and isolated cases of torsade de pointes have been reported although causality 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. (5.1, 5.5, 12.3)
- PR interval prolongation may occur in some patients. Cases of second and third degree heart block have been reported. Use with caution in patients with pre-existing conduction system disease, ischemic heart disease, cardiomyopathy, underlying structural heart disease or when administering with other drugs that may prolong the PR interval. (5.1, 5.6, 12.3)
- Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.7), immune reconstitution syndrome. (5.8), redistribution/accumulation of body fat. (5.10)
- Total cholesterol and triglycerides elevations. Monitor prior to therapy and periodically thereafter. (5.9)
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required. (5.11)

### ADVERSE REACTIONS

Commonly reported adverse reactions to lopinavir and ritonavir included diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Lannett Company, Inc. at 1-844-834-0530 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

### DRUG INTERACTIONS

Co-administration of lopinavir and ritonavir can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of lopinavir. The potential for drug-drug interactions must be considered prior to and during therapy. (4, 5.1, 7, 12.3)

### USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding not recommended. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 12/2016**

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Lopinavir and ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).

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 [see *Microbiology (12.4)* and *Clinical Studies (14)*].
- Genotypic or phenotypic testing and/or treatment history should guide the use of lopinavir and ritonavir [see *Microbiology (12.4)*]. The number of baseline lopinavir resistance-associated substitutions affects the virologic response to lopinavir and ritonavir [see *Microbiology (12.4)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 General Administration Recommendations

Lopinavir and ritonavir oral solution must be taken with food.

#### 2.2 Dosage Recommendations in Adults

Considerations in Determining Lopinavir and Ritonavir Once Daily vs. Twice Daily Dosing Regimen:

- Lopinavir and ritonavir can be given as once daily or twice daily dosing regimen in patients with less than three lopinavir resistance-associated substitutions.
- Lopinavir and ritonavir must be given as twice daily dosing regimen in patients with three or more resistance-associated substitutions.
- [Table 1](#) includes the recommended once daily dosing regimen and [Tables 2](#) and [3](#) include the recommended twice daily dosing regimen.

Lopinavir and ritonavir once daily dosing regimen is not recommended in:

- 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 [see *Microbiology (12.4)*].
- In combination with carbamazepine, phenobarbital, or phenytoin [see *Drug Interactions (7.3)*].
- In combination with efavirenz, nevirapine, or nelfinavir [see *Drug Interactions (7.3)* and *Clinical Pharmacology (12.3)*].
- In pregnant women [see *Dosage and Administration (2.4)*, *Use in Specific Populations (8.1)* and *Clinical Pharmacology (12.3)*].

The dose of lopinavir and ritonavir must be increased when administered in combination with efavirenz, nevirapine or nelfinavir.

Table 3 outlines the dosage recommendations for twice daily dosing when lopinavir and ritonavir is taken in combination with efavirenz, nevirapine or nelfinavir.

**Table 1. Recommended Dosage in Adults – Lopinavir and Ritonavir Once Daily Regimen**

<b>Lopinavir and Ritonavir Dosage Form</b>	<b>Recommended Dosage</b>
80 mg/20 mg per mL Oral Solution	800 mg/200 mg (10 mL) once daily

**Table 2. Recommended Dosage in Adults – Lopinavir and Ritonavir Twice Daily Regimen**

<b>Lopinavir and Ritonavir Dosage Form</b>	<b>Recommended Dosage</b>
80 mg/20 mg per mL Oral Solution	400 mg/100 mg (5 mL) twice daily

**Table 3. Recommended Dosage in Adults – Lopinavir and Ritonavir Twice Daily Regimen in Combination with Efavirenz, Nevirapine, or Nelfinavir**

<b>Lopinavir and Ritonavir Dosage Form</b>	<b>Recommended Dosage</b>
80 mg/20 mg per mL Oral Solution	520 mg/130 mg (6.5 mL) twice daily

### **2.3 Dosage Recommendations in Pediatric Patients**

Lopinavir and ritonavir oral solution should not be administered once daily in pediatric patients < 18 years of age. The dose of the oral solution should be administered using a calibrated dosing syringe.

Lopinavir and ritonavir oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained [*see Warnings and Precautions (5.2)*].

Lopinavir and ritonavir oral solution contains 42.4% (v/v) alcohol and 15.5% (w/v) propylene glycol. Special attention should be given to accurate calculation of the dosage of lopinavir and ritonavir, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors, and overdose. This is especially important for infants and young children. Total amounts of alcohol and propylene glycol from all medicines that are to be given to pediatric patients 14 days to 6 months of age should be taken into account in order to avoid toxicity from these excipients [*see Warnings and Precautions (5.2)* and *Overdosage (10)*].

### Pediatric Dosage Calculations

Calculate the appropriate dose of lopinavir and ritonavir for each individual pediatric patient 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:

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

The lopinavir and ritonavir dose can be calculated based on weight or BSA:

*Based on Weight:*

Patient Weight (kg)  $\times$  Prescribed lopinavir dose (mg/kg) = Administered lopinavir dose (mg)

*Based on BSA:*

Patient BSA (m<sup>2</sup>)  $\times$  Prescribed lopinavir dose (mg/m<sup>2</sup>) = Administered lopinavir dose (mg)

If lopinavir and ritonavir oral solution is used, the volume (mL) of lopinavir and ritonavir solution can be determined as follows:

Volume of lopinavir and ritonavir solution (mL) = Administered lopinavir dose (mg)  $\div$  80 (mg/mL)

### *Dosage Recommendation in Pediatric Patients 14 Days to 6 Months:*

In pediatric patients 14 days to 6 months of age, the recommended dosage of lopinavir and ritonavir using lopinavir and ritonavir oral solution is 16/4 mg/kg or 300/75 mg/m<sup>2</sup> twice daily. Prescribers should calculate the appropriate dose based on body weight or body surface area. Table 4 summarizes the recommended daily dosing regimen for pediatric patients 14 days to 6 months.

It is recommended that lopinavir and ritonavir not be administered in combination with efavirenz, nevirapine, or nelfinavir in patients < 6 months of age.

**Table 4. Recommended Lopinavir and Ritonavir Oral Daily Dosage in Pediatric Patients 14 days to 6 months**

Patient Age	Based on Weight (mg/kg)	Based on BSA (mg/m <sup>2</sup> )	Frequency
14 days to 6 months	16/4	300/75	Given twice daily

*Dosage Recommendation in Pediatric Patients > 6 Months to < 18 Years:*

Without Concomitant Efavirenz, Nevirapine, or Nelfinavir

*Dosing recommendations using oral solution*

In children > 6 months to < 18 years of age, the recommended dosage of lopinavir and ritonavir using lopinavir and ritonavir oral solution without concomitant efavirenz, nevirapine, or nelfinavir is 230/57.5 mg/m<sup>2</sup> given twice daily, not to exceed the recommended adult dose (400/100 mg [5 mL] twice daily). If weight-based dosing is preferred, the recommended dosage of lopinavir and 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. Table 5 summarizes the recommended daily dosing regimen for pediatric patients > 6 months to < 18 years.

**Table 5. Recommended Lopinavir and Ritonavir Oral Daily Dosage in Pediatric Patients > 6 months to < 18 years**

Patient Age	Based on Weight (mg/kg)		Based on BSA (mg/m <sup>2</sup> )	Frequency
> 6 months to < 18 years	<15 kg	12/3	230/57.5	Given twice daily
	≥15 kg to 40 kg	10/2.5		

Concomitant Therapy: Efavirenz, Nevirapine, or Nelfinavir

*Dosing recommendations using oral solution*

A dose increase of lopinavir and ritonavir to 300/75 mg/m<sup>2</sup> using lopinavir and ritonavir oral solution is needed when co-administered with efavirenz, nevirapine, or nelfinavir in children (both treatment-naïve and treatment-experienced) > 6 months to < 18 years of age, not to exceed the recommended adult dose (533/133 mg [6.5 mL] twice daily). 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.

## 2.4 Dosage Recommendations in Pregnancy

Administer 400/100 mg of lopinavir and ritonavir twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions. Once daily lopinavir and ritonavir dosing is not recommended in pregnancy [see *Use in Specific Populations (8.1)* and *Clinical Pharmacology (12.3)*].

- There are insufficient data to recommend dosing in pregnant women with any documented lopinavir-associated resistance substitutions.
- No dosage adjustment of lopinavir and ritonavir is required for patients during the postpartum period.
- Avoid use of lopinavir and ritonavir oral solution in pregnant women [see *Use in Specific Populations (8.1)*].

## 3 DOSAGE FORMS AND STRENGTHS

- *Lopinavir and Ritonavir Oral Solution USP*: Colorless to yellow colored liquid containing 400 mg lopinavir and 100 mg ritonavir per 5 mL (80 mg lopinavir and 20 mg ritonavir per mL).

## 4 CONTRAINDICATIONS

- Lopinavir and ritonavir is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, urticaria, angioedema) to any of its ingredients, including ritonavir.
- 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.
- Lopinavir and ritonavir is contraindicated with drugs that are 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.



**Table 8. Drugs That are Contraindicated with Lopinavir and Ritonavir**

<b>Drug Class</b>	<b>Drugs Within Class That are Contraindicated with Lopinavir and Ritonavir</b>	<b>Clinical Comments</b>
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antiarrhythmic	Dronedarone	Potential for cardiac arrhythmias.
Anti-gout	Colchicine <sup>a</sup>	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
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.
Antipsychotics	Lurasidone Pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot Derivatives	Dihydroergotamine, 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.
Hepatitis C direct acting antiviral	Elbasvir/grazoprevir	Potential for the increased risk of alanine transaminase (ALT) elevations.
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 Inhibitor	Sildenafil <sup>b</sup> (Revatio <sup>®</sup> ) when used for the treatment of pulmonary arterial hypertension	Potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope .
Sedative/Hypnotics	Triazolam; orally administered midazolam <sup>c</sup>	Prolonged or increased sedation or respiratory depression.
<sup>a</sup> see Drug Interactions (7), Table 13 for colchicine doses in patients with normal hepatic and renal function. <sup>b</sup> see Drug Interactions (7), Table 13 for co-administration of sildenafil in patients with erectile dysfunction. <sup>c</sup> see Drug Interactions (7), Table 13 for parenterally administered midazolam.		



## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of lopinavir and ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving lopinavir and ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of lopinavir and ritonavir, respectively. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of lopinavir and ritonavir.
- Loss of therapeutic effect of lopinavir and ritonavir and possible development of resistance.

See [Table 13](#) for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations [*see Drug Interactions (7)*]. Consider the potential for drug interactions prior to and during lopinavir and ritonavir therapy; review concomitant medications during lopinavir and ritonavir therapy, and monitor for the adverse reactions associated with the concomitant medications [*see Contraindications (4)* and *Drug Interactions (7)*].

### 5.2 Toxicity in Preterm Neonates

Lopinavir and ritonavir oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.5% w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving lopinavir and ritonavir oral solution.

Lopinavir and ritonavir oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of lopinavir and ritonavir oral solution in this patient population has not been established. However, if the benefit of using lopinavir and ritonavir oral solution to treat HIV infection in infants immediately after birth outweighs the potential risks, infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to Lopinavir and ritonavir oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients [see *Dosage and Administration* (2.3) and *Overdosage* (10)].

### **5.3 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* (5.9)]. 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.

### **5.4 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 [*see Use in Specific Populations (8.6)*].

### **5.5 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 [*see Clinical Pharmacology (12.3)*].

### **5.6 PR Interval Prolongation**

Lopinavir and 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 [*see Clinical Pharmacology (12.3)*].

### **5.7 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. Consider monitoring for hyperglycemia, new onset diabetes mellitus or an exacerbation of diabetes mellitus in patients treated with lopinavir and ritonavir.

### **5.8 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.

### **5.9 Lipid Elevations**

Treatment with lopinavir and ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides [see *Adverse Reactions* (6.1)]. 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* (4) and *Drug Interactions* (7.3)].

### 5.10 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.

### 5.11 Patients with Hemophilia

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.

### 5.12 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 [see *Microbiology* (12.4)].

## 6 ADVERSE REACTIONS

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

- QT Interval Prolongation, PR Interval Prolongation [see *Warnings and Precautions* (5.5, 5.6)]
- Drug Interactions [see *Warnings and Precautions* (5.1)]
- Pancreatitis [see *Warnings and Precautions* (5.3)]
- Hepatotoxicity [see *Warnings and Precautions* (5.4)]

### 6.1 Clinical Trials Experience

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.

### Adverse Reactions in Adults

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

In clinical studies the incidence of diarrhea in patients treated with either lopinavir and ritonavir capsules or tablets was greater in those patients treated once daily than in those patients treated twice daily. Any grade of diarrhea was reported by at least half of patients taking once daily lopinavir and ritonavir capsules or tablets. At the time of treatment discontinuation, 4.2-6.3% of patients taking once daily lopinavir and ritonavir and 1.8-3.7% of those taking twice daily lopinavir and ritonavir reported ongoing diarrhea.

Commonly reported adverse reactions to lopinavir and ritonavir included diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. Diarrhea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridemia and hypercholesterolemia may occur later. The following have been identified as adverse reactions of moderate or severe intensity (Table 9):

**Table 9. Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult Patients Receiving Lopinavir and Ritonavir in Combined Phase II/IV Studies (N=2,612)**

System Organ Class (SOC) and Adverse Reaction	n	%
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>		
anemia*	54	2.1
leukopenia and neutropenia*	44	1.7
lymphadenopathy*	35	1.3
<b>CARDIAC DISORDERS</b>		
atherosclerosis such as myocardial infarction*	10	0.4
atrioventricular block*	3	0.1
tricuspid valve incompetence*	3	0.1
<b>EAR AND LABYRINTH DISORDERS</b>		
vertigo*	7	0.3
tinnitus	6	0.2
<b>ENDOCRINE DISORDERS</b>		
hypogonadism*	16	0.8 <sup>1</sup>
<b>EYE DISORDERS</b>		
visual impairment*	8	0.3
<b>GASTROINTESTINAL DISORDERS</b>		
diarrhea*	510	19.5
nausea	269	10.3
vomiting*	177	6.8
abdominal pain (upper and lower)*	160	6.1

gastroenteritis and colitis*	66	2.5
dyspepsia	53	2.0
pancreatitis*	45	1.7
Gastroesophageal Reflux Disease (GERD)*	40	1.5
hemorrhoids	39	1.5
flatulence	36	1.4
abdominal distension	34	1.3
constipation*	26	1.0
stomatitis and oral ulcers*	24	0.9
duodenitis and gastritis*	20	0.8
gastrointestinal hemorrhage including rectal hemorrhage*	13	0.5
dry mouth	9	0.3
gastrointestinal ulcer*	6	0.2
fecal incontinence	5	0.2
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>		
fatigue including asthenia*	198	7.6
<b>HEPATOBIILIARY DISORDERS</b>		
hepatitis including AST, ALT, and GGT increases*	91	3.5
hepatomegaly	5	0.2
cholangitis	3	0.1
hepatic steatosis	3	0.1
<b>IMMUNE SYSTEM DISORDERS</b>		
hypersensitivity including urticaria and angioedema*	70	2.7
immune reconstitution syndrome	3	0.1
<b>INFECTIONS AND INFESTATIONS</b>		
upper respiratory tract infection*	363	13.9
lower respiratory tract infection*	202	7.7
skin infections including cellulitis, folliculitis, and furuncle*	86	3.3
<b>METABOLISM AND NUTRITION DISORDERS</b>		
hypercholesterolemia*	192	7.4
hypertriglyceridemia*	161	6.2
weight decreased*	61	2.3
decreased appetite	52	2.0
blood glucose disorders including diabetes mellitus*	30	1.1
weight increased*	20	0.8
lactic acidosis*	11	0.4
increased appetite	5	0.2
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>		
musculoskeletal pain including arthralgia and back pain*	166	6.4
myalgia*	46	1.8
muscle disorders such as weakness and spasms*	34	1.3
rhabdomyolysis*	18	0.7
osteonecrosis	3	0.1
<b>NERVOUS SYSTEM DISORDERS</b>		
headache including migraine*	165	6.3
insomnia*	99	3.8
neuropathy and peripheral neuropathy*	51	2.0
dizziness*	45	1.7
ageusia*	19	0.7
convulsion*	9	0.3
tremor*	9	0.3



cerebral vascular event*	6	0.2
<b>PSYCHIATRIC DISORDERS</b>		
anxiety*	101	3.9
abnormal dreams*	19	0.7
libido decreased	19	0.7
<b>RENAL AND URINARY DISORDERS</b>		
renal failure*	31	1.2
hematuria*	20	0.8
nephritis*	3	0.1
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>		
erectile dysfunction*	34	1.7 <sup>1</sup>
menstrual disorders - amenorrhea, menorrhagia*	10	1.7 <sup>2</sup>
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>		
rash including maculopapular rash*	99	3.8
lipodystrophy acquired including facial wasting*	58	2.2
dermatitis/rash including eczema and seborrheic dermatitis*	50	1.9
night sweats*	42	1.6
pruritus*	29	1.1
alopecia	10	0.4
capillaritis and vasculitis*	3	0.1
<b>VASCULAR DISORDERS</b>		
hypertension*	47	1.8
deep vein thrombosis*	17	0.7
*Represents a medical concept including several similar MedDRA PTs		
<sup>1</sup> Percentage of male population (N=2,038)		
<sup>2</sup> Percentage of female population (N=574)		

#### *Laboratory Abnormalities in Adults*

The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in [Table 10](#) (treatment-naïve patients) and [Table 11](#) (treatment-experienced patients).

**Table 10. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients**

		<b>Study 863 (48 Weeks)</b>		<b>Study 720 (360 Weeks)</b>	<b>Study 730 (48 Weeks)</b>	
<b>Variable</b>	<b>Limit<sup>1</sup></b>	<b>Lopinavir and Ritonavir 400/100 mg Twice Daily + d4T + 3TC (N=326)</b>	<b>Nelfinavir 750 mg Three Times Daily + d4T + 3TC (N=327)</b>	<b>Lopinavir and Ritonavir Twice Daily + d4T + 3TC (N=100)</b>	<b>Lopinavir and Ritonavir Once Daily + TDF + FTC (N=333)</b>	<b>Lopinavir and Ritonavir Twice Daily + TDF + FTC (N=331)</b>
<b>Chemistry</b>	<b>High</b>					
Glucose	>250 mg/dL	2%	2%	4%	0%	<1%
Uric Acid	>12 mg/dL	2%	2%	5%	<1%	1%
SGOT/ AST <sup>2</sup>	>180 U/L	2%	4%	10%	1%	2%
SGPT/ ALT <sup>2</sup>	>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%
<b>Chemistry</b>	<b>Low</b>					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	2%	2%
<b>Hematology</b>	<b>Low</b>					
Neutrophils	<0.75 x 10 <sup>9</sup> /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 11. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients**

		Study 888 (48 Weeks)		Study 957 <sup>2</sup> and Study 765 <sup>3</sup> (84-144 Weeks)	Study 802 (48 Weeks)	
Variable	Limit <sup>1</sup>	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)
<b>Chemistry</b>	<b>High</b>					
Glucose	>250 mg/dL	1%	2%	5%	2%	2%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%	1%	1%
SGOT/AST <sup>4</sup>	>180 U/L	5%	11%	8%	3%	2%
SGPT/ALT <sup>4</sup>	>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%
<b>Chemistry</b>	<b>Low</b>					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	3%	3%
Inorganic Phosphorus	<1.5 mg/dL	1%	0%	2%	1%	<1%
<b>Hematology</b>	<b>Low</b>					
Neutrophils	<0.75 x 10 <sup>9</sup> /L	1%	2%	4%	3%	4%
Hemoglobin	<80 g/L	1%	1%	1%	1%	2%
<sup>1</sup> ULN = upper limit of the normal range; N/A = Not Applicable. <sup>2</sup> 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. <sup>3</sup> 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. <sup>4</sup> Criterion for Study 802 was >5x ULN (AST/ALT).						

### Adverse Reactions in Pediatric Patients

Lopinavir and ritonavir oral solution dosed up to 300/75 mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> (without concomitant NNRTI) and 480/120 mg/m<sup>2</sup> (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 in Pediatric Patients*

The percentages of pediatric patients treated with combination therapy including lopinavir and ritonavir with Grade 3-4 laboratory abnormalities are presented in [Table 12](#).

**Table 12. Grade 3-4 Laboratory Abnormalities Reported in  $\geq 2\%$  Pediatric Patients in Study 940**

Variable	Limit <sup>1</sup>	Lopinavir and Ritonavir Twice Daily + RTIs (N=100)
<b>Chemistry</b>	<b>High</b>	
Sodium	>149 mEq/L	3%
Total Bilirubin	$\geq 3.0 \times \text{ULN}$	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% <sup>2</sup>
<b>Chemistry</b>	<b>Low</b>	
Sodium	<130 mEq/L	3%
<b>Hematology</b>	<b>Low</b>	
Platelet Count	<50 x 10 <sup>9</sup> /L	4%
Neutrophils	<0.40 x 10 <sup>9</sup> /L	2%
<sup>1</sup> ULN = upper limit of the normal range. <sup>2</sup> Subjects with Grade 3-4 amylase confirmed by elevations in pancreatic amylase.		

## 6.2 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 (5.10)*].

### 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 (5.5, 5.6)*].

### Skin and Appendages

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

## 7 DRUG INTERACTIONS

*See also Contraindications (4), Warnings and Precautions (5.1), Clinical Pharmacology (12.3)*

### 7.1 Potential for Lopinavir and Ritonavir to Affect Other Drugs

Lopinavir and 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 13.

Additionally, lopinavir and ritonavir induces glucuronidation.

Published data suggest that lopinavir is an inhibitor of OATP1B1.

### 7.2 Potential for Other Drugs to Affect Lopinavir

Lopinavir and 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.

### 7.3 Established and Other Potentially Significant Drug Interactions

Table 13 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 [see *Clinical Pharmacology (12.3)*] for magnitude of interaction.

**Table 13. Established and Other Potentially Significant Drug Interactions**

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comments
<b><i>HIV-1 Antiviral Agents</i></b>		
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 once daily in combination with nelfinavir is not recommended [see <i>Dosage and Administration (2)</i> ].
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	Co-administration with tipranavir (500 mg twice daily) and ritonavir (200 mg twice daily) is not recommended.
HIV CCR5 – Antagonist: maraviroc*	↑ 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	Increase the dose of lopinavir and ritonavir tablets to 500/125 mg when lopinavir and ritonavir tablet is co-administered with efavirenz or nevirapine. Lopinavir and ritonavir once daily in combination with efavirenz or nevirapine is not recommended [see Dosage and Administration (2)].
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		For lopinavir and ritonavir oral solution, it is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after lopinavir and ritonavir oral solution (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir disoproxil fumarate*	↑ tenofovir	Patients receiving lopinavir and ritonavir and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside Reverse Transcriptase Inhibitors: abacavir zidovudine	↓ abacavir ↓ zidovudine	The clinical significance of this potential interaction is unknown.
<b>Other Agents</b>		
Antiarrhythmics e.g. amiodarone, bepridil, lidocaine (systemic), quinidine	↑ antiarrhythmics	For contraindicated antiarrhythmics, [see Contraindications (4)]. 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	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.



Anticoagulants: warfarin,  rivaroxaban	↑↓ warfarin  ↑ rivaroxaban	Concentrations of warfarin may be affected. Initial frequent monitoring of the INR during lopinavir and ritonavir and warfarin co-administration is recommended. Avoid concomitant use of rivaroxaban and lopinavir and ritonavir. Co-administration of lopinavir and ritonavir and rivaroxaban 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 once daily in combination with carbamazepine, phenobarbital, or phenytoin is not recommended. 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	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	Patients receiving lopinavir and ritonavir and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	For patients with renal impairment, adjust clarithromycin dose as follows: <ul style="list-style-type: none"> <li>For patients on lopinavir and ritonavir with <math>CL_{CR}</math> 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.</li> <li>For patients on lopinavir and ritonavir with <math>CL_{CR}</math> &lt; 30 mL/min the dose of clarithromycin should be decreased by 75%.</li> </ul> No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole, voriconazole isavuconazonium sulfate*	↑ ketoconazole ↑ itraconazole ↓ voriconazole ↑ isavuconazonium	High doses of ketoconazole (>200 mg/day) or itraconazole (> 200 mg/day) are not recommended. The co-administration of voriconazole and lopinavir and ritonavir should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Isavuconazonium and lopinavir and ritonavir should be co-administered with caution. Alternative antifungal therapies should be considered in these patients.
Anti-gout: colchicine	↑ colchicine	Concomitant administration with colchicine is contraindicated in patients with renal and/or hepatic impairment [see <i>Contraindications</i> (4)]. <u>For patients with normal renal or hepatic function:</u> <i>Treatment of gout flares-co-administration of colchicine in patients on lopinavir and ritonavir:</i> 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.

		<p><i>Prophylaxis of gout flares-co-administration of colchicine in patients on lopinavir and ritonavir:</i> 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><i>Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on lopinavir and ritonavir:</i> Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p>
Antimycobacterial: bedaquiline	↑ bedaquiline	For contraindicated antimycobacterials, [see <i>Contraindications (4)</i> ]. Bedaquiline should only be used with lopinavir and ritonavir if the benefit of co-administration outweighs the risk.
Antimycobacterial: rifabutin*	↑ rifabutin and rifabutin metabolite	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.
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Antipsychotics: quetiapine	↑ quetiapine	<p><u>Initiation of lopinavir and ritonavir in patients taking quetiapine:</u> Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring.</p> <p><u>Initiation of quetiapine in patients taking lopinavir and ritonavir:</u> Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.</p>
Sedative/hypnotics: parenterally administered midazolam	↑ midazolam	For contraindicated sedative/hypnotics, [see <i>Contraindications (4)</i> ]. 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 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	Clinical monitoring of patients is recommended and a dose reduction of the dihydropyridine calcium channel blocker may be considered.
Disulfiram/metronidazole		Lopinavir and 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).
Endothelin Receptor Antagonists: bosentan	↑ bosentan	<u>Co-administration of bosentan in patients on lopinavir and ritonavir:</u> 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. <u>Co-administration of lopinavir and ritonavir in patients on bosentan:</u> 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.
Hepatitis C direct acting antivirals: boceprevir*  simeprevir  ombitasvir/parataprevir/ritonavir and dasabuvir*	↓ lopinavir ↓ boceprevir ↓ ritonavir  ↑ simeprevir  ↑ ombitasvir ↑ parataprevir ↑ ritonavir ↔ dasabuvir	For contraindicated hepatitis C direct acting antivirals, [see <i>Contraindications (4)</i> ]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, simeprevir, or ombitasvir/parataprevir/ritonavir and dasabuvir.
HMG-CoA Reductase Inhibitors: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	For contraindicated HMG-CoA reductase inhibitors, [see <i>Contraindications (4)</i> ]. 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.
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 ritonavir-containing 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 Analgesics: methadone,* fentanyl	↓ methadone ↑ fentanyl	Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. 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	<p>For contraindicated PDE5 inhibitors, [see <i>Contraindications (4)</i>].</p> <p>Do not use lopinavir and ritonavir with avanafil because a safe and effective avanafil dosage regimen has not been established.</p> <p>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 may result in an increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection.</p> <p>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):</p> <p>Sildenafil (Revatio®) is contraindicated [see <i>Contraindications (4)</i>].</p> <p>The following dose adjustments are recommended for use of tadalafil (Adcirca®) with lopinavir and ritonavir:</p> <p><u>Co-administration of ADCIRCA in patients on lopinavir and ritonavir:</u></p> <p>In patients receiving lopinavir and ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Co-administration of lopinavir and ritonavir in patients on ADCIRCA:</u></p> <p>Avoid use of ADCIRCA during the initiation of lopinavir and ritonavir. Stop ADCIRCA at least 24 hours prior to starting lopinavir and ritonavir. After at least one week following the initiation of lopinavir and ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p>Use of PDE5 inhibitors for erectile dysfunction:</p> <p>It is recommended not to exceed the following doses:</p> <ul style="list-style-type: none"> <li>• Sildenafil: 25 mg every 48 hours</li> <li>• Tadalafil: 10 mg every 72 hours</li> <li>• Vardenafil: 2.5 mg every 72 hours</li> </ul> <p>Use with increased monitoring for adverse events.</p>

\* see *Clinical Pharmacology (12.3)* for magnitude of interaction.

#### 7.4 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), etravirine, pitavastatin, pravastatin, stavudine, lamivudine, omeprazole, raltegravir, ranitidine, or rilpivirine.

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to lopinavir and ritonavir during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263.

##### Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits; however embryonic and fetal developmental toxicities occurred in rats administered maternally toxic doses.

##### Clinical Considerations

##### *Dose Adjustments During Pregnancy and the Postpartum Period*

Administer 400/100 mg of lopinavir and ritonavir twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*]. There are insufficient data to recommend lopinavir and ritonavir dosing for pregnant patients with any documented lopinavir-associated resistance substitutions. No dose adjustment of lopinavir and ritonavir is required for patients during the postpartum period.

Once daily lopinavir and ritonavir dosing is not recommended in pregnancy.

Avoid use of lopinavir and ritonavir oral solution during pregnancy due to the alcohol content. Lopinavir and ritonavir oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.5% w/v).

## Data

### *Human Data*

Lopinavir and ritonavir was evaluated in 12 HIV-infected pregnant women in an open-label pharmacokinetic trial [see *Clinical Pharmacology* (12.3)]. No new trends in the safety profile were identified in pregnant women dosed with lopinavir and ritonavir compared to the safety described in non-pregnant adults, based on the review of these limited data.

Antiretroviral Pregnancy Registry Data: Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of over 3,000 exposures to lopinavir containing regimens (including over 1,000 exposed in the first trimester), there was no difference between lopinavir and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. Based on prospective reports from the APR of over 5,000 exposures to ritonavir containing regimens (including over 2,000 exposures in the first trimester) there was no difference between ritonavir and overall birth defects compared with the U.S. background rate (MACDP). For both lopinavir and ritonavir, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5 fold increase in risk of overall birth defects and a 2 fold increase in risk of birth defects in the cardiovascular and genitourinary systems.

### *Animal Data*

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).

## **8.2 Lactation**

### Risk Summary

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. Because of the potential for HIV-1 transmission in breastfed infants, advise women not to breastfeed.



#### 8.4 Pediatric Use

The safety, efficacy, and pharmacokinetic profiles of lopinavir and ritonavir in pediatric patients below the age of 14 days have not been established. Lopinavir and ritonavir should not be administered once daily in pediatric patients.

An open-label, multi-center, dose-finding trial was performed to evaluate the pharmacokinetic profile, tolerability, safety and efficacy of lopinavir and ritonavir oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of 300/75 mg/m<sup>2</sup> twice daily plus two NRTIs in HIV-infected infants  $\geq 14$  days and  $< 6$  months of age. Results revealed that infants younger than 6 months of age generally had lower lopinavir AUC<sub>12</sub> than older children (6 months to 12 years of age), however, despite the lower lopinavir drug exposure observed, antiviral activity was demonstrated as reflected in the proportion of subjects who achieved HIV-1 RNA  $< 400$  copies/mL at Week 24 [*see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)*].

Safety and efficacy in pediatric patients  $> 6$  months of age was demonstrated in a clinical trial in 100 patients. The clinical trial was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety, and efficacy of lopinavir and ritonavir oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naïve and experienced pediatric patients ages 6 months to 12 years. Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m<sup>2</sup> oral solution twice daily regimen without nevirapine and the 300/75 mg/m<sup>2</sup> oral solution twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine) [*see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)*].

A prospective multicenter, open-label trial evaluated the pharmacokinetic profile, tolerability, safety and efficacy of high-dose lopinavir and ritonavir with or without concurrent NNRTI therapy (Group 1: 400/100 mg/m<sup>2</sup> twice daily +  $\geq 2$  NRTIs; Group 2: 480/120 mg/m<sup>2</sup> twice daily +  $\geq 1$  NRTI + 1 NNRTI) in 26 children and adolescents  $\geq 2$  years to  $< 18$  years of age who had failed prior therapy. Patients also had saquinavir mesylate added to their regimen. This strategy was intended to assess whether higher than approved doses of lopinavir and ritonavir could overcome protease inhibitor cross-resistance. High doses of lopinavir and ritonavir exhibited a safety profile similar to those observed in previous trials; changes in HIV-1 RNA were less than anticipated; three patients had HIV-1 RNA  $< 400$  copies/mL at Week 48. CD4<sup>+</sup> cell count increases were noted in the eight patients who remained on treatment for 48 weeks [*see Adverse Reactions (6.2), Clinical Pharmacology (12.3)*].



### 8.5 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.

### 8.6 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 [*see Warnings and Precautions (5.4)* and *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

Overdoses with lopinavir and ritonavir oral solution have been reported. One of these reports described fatal cardiogenic shock in a 2.1 kg infant who received a single dose of 6.5 mL of lopinavir and ritonavir oral solution (520 mg lopinavir, approximately 10-fold above the recommended lopinavir dose) nine days prior. The following events have been reported in association with unintended overdoses in preterm neonates: complete AV block, cardiomyopathy, lactic acidosis, and acute renal failure [*see Warnings and Precautions (5.2)*]. Healthcare professionals should be aware that lopinavir and ritonavir oral solution is highly concentrated and therefore, should pay special attention 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. This is especially important for infants and young children.

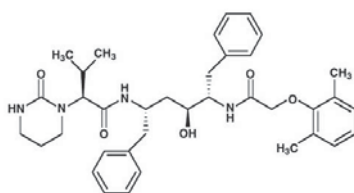
Lopinavir and ritonavir oral solution contains 42.4% alcohol (v/v) and 15.5% propylene glycol (w/v). Ingestion of the product over the recommended dose by an infant or a young child could result in significant toxicity and could potentially be lethal.

Human experience of acute overdose 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. However, dialysis can remove both alcohol and propylene glycol in the case of overdose with lopinavir and ritonavir oral solution.

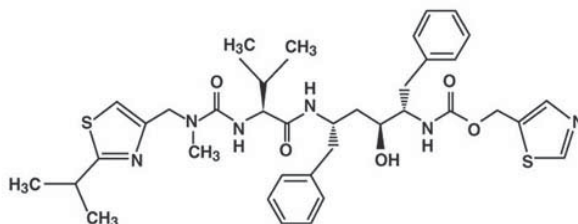
## 11 DESCRIPTION

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

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



Ritonavir is chemically designated as 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5*S*-(5*R*\*, 8*R*\*, 10*R*\*, 11*R*\*)]. Its molecular formula is  $C_{37}H_{48}N_6O_5S_2$ , and its molecular weight is 720.95. Ritonavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water. Ritonavir has the following structural formula:



Lopinavir and ritonavir oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: alcohol, bubble gum flavor, glycerin, high fructose corn syrup, malic acid, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, sodium hydroxide, sucralose, and water.

Lopinavir and ritonavir oral solution contains 42.4% alcohol (v/v).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

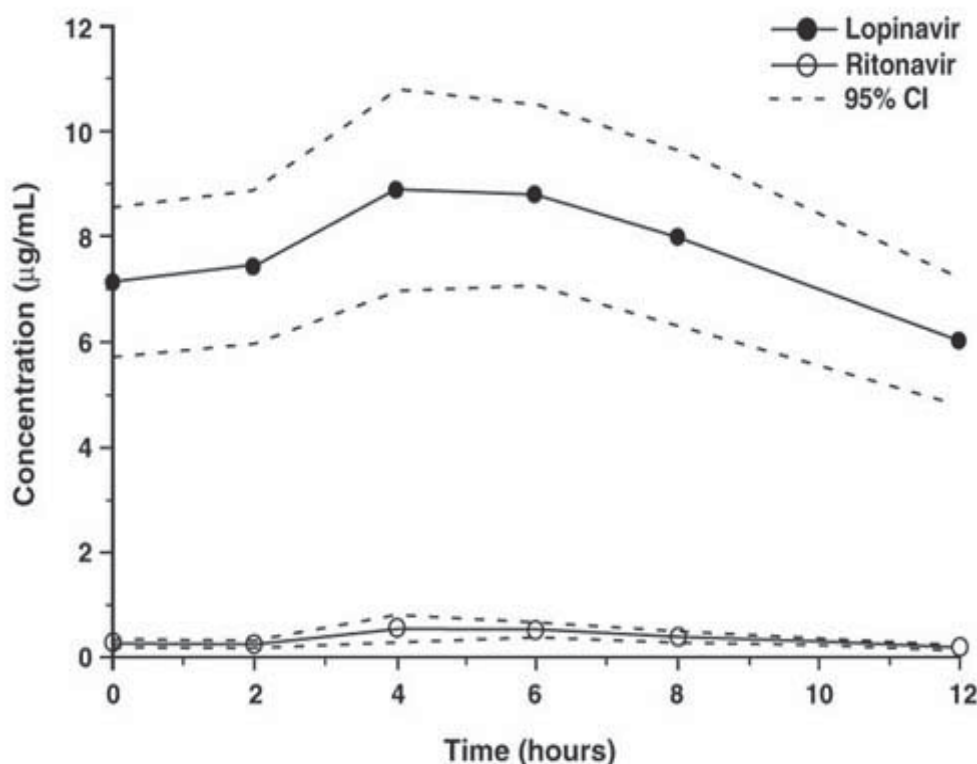
Lopinavir is an antiviral drug [see *Microbiology* (12.4)]. As co-formulated in lopinavir and ritonavir, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

### 12.3 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<sub>50</sub> 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) Absorption**



### **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  $\pm$  SD lopinavir peak plasma concentration ( $C_{max}$ ) of  $9.8 \pm 3.7$  µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was  $7.1 \pm 2.9$  µg/mL and minimum concentration within a dosing interval was  $5.5 \pm 2.7$  µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged  $92.6 \pm 36.7$  µg•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 and 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 and ritonavir oral solution relative to the capsule formulation.

Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg 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 Oral Solution USP

Relative to fasting, administration of lopinavir and ritonavir oral solution with a moderate fat meal (500 - 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and  $C_{max}$  by 80 and 54%, respectively. Relative to fasting, administration of lopinavir and ritonavir oral solution with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC and  $C_{max}$  by 130% and 56%, respectively. To enhance bioavailability and minimize pharmacokinetic variability lopinavir and ritonavir oral solution should be taken with 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  $^{14}\text{C}$ -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  $^{14}\text{C}$ -lopinavir and ritonavir dose, approximately  $10.4 \pm 2.3\%$  and  $82.6 \pm 2.5\%$  of an administered dose of  $^{14}\text{C}$ -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  $5.98 \pm 5.75$  L/hr (mean  $\pm$  SD, n = 19).

### Once Daily Dosing

The pharmacokinetics of once daily lopinavir and ritonavir have been evaluated in HIV-1 infected subjects naïve 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  $\pm$  SD lopinavir peak plasma concentration ( $C_{\max}$ ) of  $11.8 \pm 3.7$   $\mu\text{g/mL}$ , occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was  $3.2 \pm 2.1$   $\mu\text{g/mL}$  and minimum concentration within a dosing interval was  $1.7 \pm 1.6$   $\mu\text{g/mL}$ . Lopinavir AUC over a 24 hour dosing interval averaged  $154.1 \pm 61.4$   $\mu\text{g}\cdot\text{h/mL}$ .

The pharmacokinetics of once daily lopinavir and ritonavir has also been evaluated in treatment experienced HIV-1 infected subjects. Lopinavir exposure ( $C_{\max}$ ,  $\text{AUC}_{[0-24\text{h}]}$ ,  $C_{\text{trough}}$ ) 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) mseconds (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 (5.5, 5.6)*].

### 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*

The pharmacokinetics of lopinavir and ritonavir oral solution 300/75 mg/m<sup>2</sup> twice daily and 230/57.5 mg/m<sup>2</sup> twice daily have been studied in a total of 53 pediatric patients in Study 940, ranging in age from 6 months to 12 years [see *Clinical Studies* (14.4)]. The 230/57.5 mg/m<sup>2</sup> twice daily regimen without nevirapine and the 300/75 mg/m<sup>2</sup> twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine).

The mean steady-state lopinavir AUC, C<sub>max</sub>, and C<sub>min</sub> were 72.6 ± 31.1 µg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 µg/mL, respectively after lopinavir and ritonavir oral solution 230/57.5 mg/m<sup>2</sup> twice daily without nevirapine (n = 12), and were 85.8 ± 36.9 µg•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5 µg/mL, respectively, after 300/75 mg/m<sup>2</sup> twice daily with nevirapine (n = 12). The nevirapine regimen was 7 mg/kg twice daily (6 months to 8 years) or 4 mg/kg twice daily (> 8 years).

The pharmacokinetics of lopinavir and ritonavir oral solution at approximately 300/75 mg/m<sup>2</sup> twice daily have also been evaluated in infants at approximately 6 weeks of age (n = 9) and between 6 weeks and 6 months of age (n = 18) in Study 1030. The mean steady-state lopinavir AUC<sub>12</sub>, C<sub>max</sub>, and C<sub>12</sub> were 43.4 ± 14.8 µg•h/mL, 5.2 ± 1.8 µg/mL and 1.9 ± 1.1 µg/mL, respectively, in infants at approximately 6 weeks of age, and 74.5 ± 37.9 µg•h/mL, 9.4 ± 4.9 and 3.1 ± 1.8 µg/mL, respectively, in infants between 6 weeks and 6 months of age after lopinavir and ritonavir oral solution was administered at approximately 300/75 mg/m<sup>2</sup> twice daily without concomitant NNRTI therapy.

The pharmacokinetics of lopinavir and ritonavir soft gelatin capsule and oral solution (Group 1: 400/100 mg/m<sup>2</sup> twice daily + 2 NRTIs; Group 2: 480/120 mg/m<sup>2</sup> twice daily + ≥ 1 NRTI + 1 NNRTI) have been evaluated in children and adolescents age ≥ 2 years to < 18 years of age who had failed prior therapy (n=26) in Study 1038. Lopinavir and ritonavir doses of 400/100 and 480/120 mg/m<sup>2</sup> resulted in high lopinavir exposure, as almost all subjects had lopinavir AUC<sub>12</sub> above 100 µg•h/mL. Both groups of subjects also achieved relatively high average minimum lopinavir concentrations.



### *Pregnancy*

In an open-label pharmacokinetic study, 12 HIV-infected pregnant women received lopinavir and ritonavir 400 mg/100 mg (two 200/50 mg tablets) twice daily as part of an antiretroviral regimen. Plasma concentrations of lopinavir were measured over 12-hour periods during the second trimester (20-24 weeks gestation), the third trimester (30 weeks gestation) and at 8 weeks post-partum. The  $C_{12h}$  values of lopinavir were lower during the second and third trimester by approximately 40% as compared to post-partum, but this decrease is not considered clinically relevant in patients with no documented lopinavir and ritonavir-associated resistance substitutions receiving 400 mg/100 mg twice daily.

### *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 (5.4)* and *Use in Specific Populations (8.6)*].

### Drug Interactions

Lopinavir and ritonavir is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of lopinavir and ritonavir and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects [see *Contraindications (4)* and *Drug Interactions (7)*].

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

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

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

Drug interaction studies were performed with lopinavir and ritonavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of lopinavir and ritonavir on the AUC,  $C_{max}$  and  $C_{min}$  are summarized in Table 14 (effect of other drugs on lopinavir) and Table 15 (effect of lopinavir and ritonavir on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see Table 13 in *Drug Interactions* (7).

**Table 14. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug for Recommended Alterations in Dose or Regimen**

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Lopinavir and Ritonavir (mg)	n	Ratio (in combination with Co-administered drug/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				$C_{max}$	AUC	$C_{min}$
Boceprevir	800 q8h, 6 d	400/100 tablet twice daily, 22 d	13	0.70 (0.65, 0.77)	0.66 <sup>12</sup> (0.60, 0.72)	0.57 (0.49, 0.65)
Efavirenz <sup>1,2</sup>	600 at bedtime, 9 d	400/100 capsule twice daily, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 at bedtime, 9 d	500/125 tablet twice daily, 10 d	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 at bedtime, 9 d	600/150 tablet twice daily, 10 d	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Elbasvir/ grazoprevir <sup>14</sup>	50 once daily, 7 d	400/100 twice daily, 21 d	9	1.02 (0.92, 1.13)	1.02 (0.93, 1.13)	1.07 (0.97, 1.18)
	200 once daily, 7 d		13	0.97 (0.88, 1.08)	1.03 (0.96, 1.16)	0.97 (0.81, 1.15)
Etravirine	200 twice daily	400/100 mg twice day (tablets)	16	0.89 (0.82-0.96)	0.87 (0.83-0.92)	0.80 (0.73-0.88)
Fosamprenavir <sup>3</sup>	700 twice daily plus ritonavir 100 twice daily, 14 d	400/100 capsule twice daily, 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole	200 single dose	400/100 capsule twice daily, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 twice daily, 10 d	400/100 capsule twice daily, 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)

Nevirapine	200 twice daily, steady-state (> 1 yr) <sup>4#</sup>	400/100 capsule twice daily, steady-state	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg once daily, 2 wk; twice daily 1 wk <sup>5</sup>	(> 1 yr) 300/75 mg/m <sup>2</sup> oral solution twice daily, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir	25/150/100 + dasabuvir 400, 28 d	400/100 tablet twice daily, 14 d	6	0.87 (0.76, 0.99)	0.94 (0.81, 1.10)	1.15 (0.93, 1.42)
Omeprazole	40 once daily, 5 d	400/100 tablet twice daily, 10 d	12	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)
	40 once daily, 5 d	800/200 tablet once daily, 10 d	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
Pitavastatin <sup>6</sup>	4 once daily, 5 d	400/100 tablet twice daily, 16 d	23	0.93 (0.88-0.98)	0.91 (0.86-0.97)	N/A
Pravastatin	20 once daily, 4 d	400/100 capsule twice daily, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 once daily, 10 d	400/100 capsule twice daily, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Ranitidine	150 single dose	400/100 tablet twice daily, 10 d	12	0.99 (0.95, 1.03)	0.97 (0.93, 1.01)	0.90 (0.85, 0.95)
	150 single dose	800/200 tablet once daily, 10 d	10	0.97 (0.95, 1.00)	0.95 (0.91, 0.99)	0.82 (0.74, 0.91)
Rifampin	600 once daily, 10 d	400/100 capsule twice daily, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 once daily, 14 d	800/200 capsule twice daily, 9 d <sup>7</sup>	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 once daily, 14 d	400/400 capsule twice daily, 9 d <sup>8</sup>	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
Rilpivirine	150 once daily <sup>13</sup>	400/100 twice daily (capsules)	15	0.96 (0.88-1.05)	0.99 (0.89-1.10)	0.89 (0.73-1.08)
Ritonavir <sup>4</sup>	100 twice daily, 3-4 wk <sup>#</sup>	400/100 capsule twice daily, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir disoproxil fumarate <sup>9</sup>	300 once daily, 14 d	400/100 capsule twice daily, 14 d	24	NC <sup>†</sup>	NC <sup>†</sup>	NC <sup>†</sup>
Tipranavir/ ritonavir <sup>4</sup>	500/200 twice daily (28 doses) <sup>#</sup>	400/100 capsule twice daily (27 doses)	21 69	0.53 (0.40, 0.69) <sup>10</sup>	0.45 (0.32, 0.63) <sup>10</sup>	0.30 (0.17, 0.51) <sup>10</sup> , 0.48 (0.40, 0.58) <sup>11</sup>

All interaction studies conducted in healthy, HIV-1 negative subjects unless otherwise indicated.

1 The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

2 Reference for comparison is lopinavir and ritonavir 400/100 mg twice daily without efavirenz.

3 Data extracted from the fosamprenavir package insert.

4 Study conducted in HIV-1 positive adult subjects.

5 Study conducted in HIV-1 positive pediatric subjects ranging in age from 6 months to 12 years.

6 Data extracted from the pitavastatin package insert and results presented at the 2011 International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (Morgan, *et al*, poster #MOPE170).

7 Titrated to 800/200 twice daily as 533/133 twice daily x 1 d, 667/167 twice daily x 1 d, then 800/200 twice daily x 7 d, compared to 400/100 twice daily x 10 days alone.

8 Titrated to 400/400 twice daily as 400/200 twice daily x 1 d, 400/300 twice daily x 1 d, then 400/400 twice daily x 7 d, compared to 400/100 twice daily x 10 days alone.  
9 Data extracted from the tenofovir package insert.  
10 Intensive PK analysis.  
11 Drug levels obtained at 8-16 hrs post-dose.  
12 AUC parameter is AUC<sub>(0-last)</sub>  
13 This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the co-administered drug.  
\* Parallel group design; n for lopinavir and ritonavir + co-administered drug, n for lopinavir and ritonavir alone.  
N/A = Not available.  
† NC = No change.  
# For the nevirapine 200 mg twice daily study, ritonavir, and tipranavir/ritonavir studies, lopinavir and ritonavir was administered with or without food. For all other studies, lopinavir and ritonavir was administered with food.

**Table 15. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of Lopinavir and Ritonavir for Recommended Alterations in Dose or Regimen**

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Lopinavir and Ritonavir (mg)	n	Ratio (in combination with Lopinavir and Ritonavir/alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C <sub>max</sub>	AUC	C <sub>min</sub>
Bedaquiline <sup>1</sup>	400 single dose	400/100 twice daily, 24 d	N/A	N/A	1.22 (1.11, 1.34)	N/A
Boceprevir	800 q8h, 6 d	400/100 tablet twice daily, 22 d	13 <sup>9</sup>	0.50 (0.45, 0.55)	0.55 (0.49, 0.61)	0.43 (0.36, 0.53)
Desipramine <sup>3</sup>	100 single dose	400/100 capsule twice daily, 10 d	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	N/A
Efavirenz	600 at bedtime, 9 d	400/100 capsule twice daily, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Elbasvir/ grazoprevir <sup>11</sup>	50 once daily, 7 d	400/100 twice daily, 21 d	10	2.87 (2.29, 3.58)	3.71 (3.05, 4.53)	4.58 (3.72, 5.64)
	200 once daily, 7 d		13	7.31 (5.65, 9.45)	12.86 (10.25, 16.13)	21.70 (12.99, 36.25)
Ethinyl Estradiol	35 µg once daily, 21 d (Ortho Novum <sup>®</sup> )	400/100 capsule twice daily, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Etravirine	200 twice daily	400/100 twice day (tablets)	16	0.70 (0.64-0.78)	0.65 (0.59-0.71)	0.55 (0.49-0.62)
Fosamprenavir <sup>4</sup>	700 twice daily plus ritonavir 100 twice daily, 14 d	400/100 capsule twice daily, 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir <sup>2</sup>	600 twice daily, 10 d combo nonfasting vs. 800 three times daily, 5 d alone fasting	400/100 capsule twice daily, 15 d	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 capsule twice daily, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Maraviroc <sup>13</sup>	300 twice daily	400/100 twice daily	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)

Methadone	5 single dose	400/100 capsule twice daily, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nelfinavir <sup>2</sup>	1000 twice daily, 10 d combo vs. 1250 twice daily 14 d alone	400/100 capsule twice daily, 21 d	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)
M8 metabolite				2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)
Nevirapine	200 once daily, 14 d; twice daily, 6 d	400/100 capsule twice daily, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 once daily, 21 d (Ortho Novum <sup>®</sup> )	400/100 capsule twice daily, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir	25/150/100 + dasabuvir 400, 28 d	400/100 tablet twice daily, 14 d	6	1.14 (1.01, 1.28)	1.17 (1.07, 1.28)	1.24 (1.14, 1.34)
				2.04 (1.30, 3.20)	2.17 (1.63, 2.89)	2.36 (1.00, 5.55)
				1.55 (1.16, 2.09)	2.05 (1.49, 2.81)	5.25 (3.33, 8.28)
				0.99 (0.75, 1.31)	0.93 (0.75, 1.15)	0.68 (0.57, 0.80)
Pitavastatin <sup>5</sup>	4 once daily, 5 d	400/100 tablet twice daily, 16 d	23	0.96 (0.84-1.10)	0.80 (0.73-0.87)	N/A
Pravastatin	20 once daily, 4 d	400/100 capsule twice daily, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	150 once daily, 10 d; combo vs. 300 once daily, 10 d; alone	400/100 capsule twice daily, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25- <i>O</i> -desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25- <i>O</i> -desacetyl rifabutin <sup>6</sup>				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Rilpivirine	150 once daily <sup>10</sup>	400/100 twice daily (capsules)	15	1.29 (1.18-1.40)	1.52 (1.36-1.70)	1.74 (1.46-2.08)
Rosuvastatin <sup>7</sup>	20 once daily, 7 d	400/100 tablet twice daily, 7 d	15	4.66 (3.4, 6.4)	2.08 (1.66, 2.6)	1.04 (0.9, 1.2)
Tenofovir alafenamide <sup>12</sup>	10 once daily	800/200 tablet once daily	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	N/A
Tenofovir disoproxil fumarate <sup>8</sup>	300 once daily, 14 d	400/100 capsule twice daily, 14 d	24	NC <sup>†</sup>	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

All interaction studies conducted in healthy, HIV-1 negative subjects unless otherwise indicated.

1 Data extracted from the bedaquiline package insert.

2 Ratio of parameters for indinavir, and nelfinavir, are not normalized for dose.

3 Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.

4 Data extracted from the fosamprenavir package insert.

5 Data extracted from the pitavastatin package insert and results presented at the 2011 International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (Morgan, *et al*, poster #MOPE170).

6 Effect on the dose-normalized sum of rifabutin parent and 25-*O*-desacetyl rifabutin active metabolite.

7 Kiser, et al. J Acquir Immune Defic Syndr. 2008 Apr 15;47(5):570-8.

8 Data extracted from the tenofovir package insert.

9 N=12 for C<sub>min</sub> (test arm)

10 This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the co-administered drug.  
11 Data extracted from the elbasvir/grazoprevir package insert  
12 Data extracted from the tenofovir alafenamide/emtricitabine package insert  
13 Data extracted from the maraviroc package insert.  
\* Parallel group design; n for lopinavir and ritonavir + co-administered drug, n for co-administered drug alone.  
N/A = Not available.  
† NC = No change.

## 12.4 Microbiology

### Mechanism of Action

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.

### Antiviral Activity

The antiviral activity of lopinavir against laboratory HIV strains and clinical HIV-1 isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC<sub>50</sub>) values of lopinavir against five different HIV-1 subtype B laboratory strains ranged from 10-27 nM (0.006-0.017 µg/mL, 1 µg/mL = 1.6 µM) and ranged from 4-11 nM (0.003-0.007 µg/mL) against several HIV-1 subtype B clinical isolates (n = 6). In the presence of 50% human serum, the mean EC<sub>50</sub> values of lopinavir against these five HIV-1 laboratory strains ranged from 65-289 nM (0.04-0.18 µg/mL), representing a 7 to 11-fold attenuation. Combination antiviral drug activity studies with lopinavir in cell cultures demonstrated additive to antagonistic activity with nelfinavir and additive to synergistic activity with amprenavir, atazanavir, indinavir, saquinavir and tipranavir. The EC<sub>50</sub> values of lopinavir against three different HIV-2 strains ranged from 12-180 nM (0.008-113 µg/mL).

### Resistance

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

The selection of resistance to lopinavir and ritonavir in antiretroviral treatment naïve patients has not yet been characterized. In a study of 653 antiretroviral treatment naïve patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV-1 RNA > 400 copies/mL at Week 24, 32, 40 and/or 48 were analyzed. No evidence of resistance to lopinavir and ritonavir was observed in 37 evaluable lopinavir and ritonavir-treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M substitution in HIV-1 protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to lopinavir and ritonavir in antiretroviral treatment naïve pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

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

#### Cross-resistance - Preclinical Studies

Varying degrees of cross-resistance have been observed among HIV-1 protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during lopinavir and ritonavir therapy.

The antiviral activity in cell culture of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed > 4-fold reduced susceptibility to nelfinavir (n = 13) and saquinavir (n = 4), displayed < 4-fold reduced susceptibility to lopinavir. Isolates with > 4-fold reduced susceptibility to indinavir (n = 16) and ritonavir (n = 3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.



### Clinical Studies - Antiviral Activity of Lopinavir and Ritonavir in Patients with Previous Protease Inhibitor Therapies

The clinical relevance of reduced susceptibility in cell culture to lopinavir has been examined by assessing the virologic response to lopinavir and ritonavir therapy in treatment-experienced patients, with respect to baseline viral genotype in three studies and baseline viral phenotype in one study.

Virologic response to lopinavir and ritonavir has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. Table 16 shows the 48-week virologic response (HIV-1 RNA <400 copies/mL) according to the number of the above protease inhibitor resistance-associated substitutions at baseline in studies 888 and 765 [see *Clinical Studies* (14.2) and (14.3)] and study 957 (see below). Once daily administration of lopinavir and ritonavir for adult patients with three or more of the above substitutions is not recommended.

**Table 16. Virologic Response (HIV-1 RNA <400 copies/mL) at Week 48 by Baseline Lopinavir and Ritonavir Susceptibility and by Number of Protease Substitutions Associated with Reduced Response to Lopinavir and Ritonavir<sup>1</sup>**

Number of protease inhibitor substitutions at baseline <sup>1</sup>	Study 888 (Single protease inhibitor-experienced <sup>2</sup> , NNRTI-naïve) n=130	Study 765 (Single protease inhibitor-experienced <sup>3</sup> , NNRTI-naïve) n=56	Study 957 (Multiple protease inhibitor-experienced <sup>4</sup> , NNRTI-naïve) n=50
0-2	76/103 (74%)	34/45 (76%)	19/20 (95%)
3-5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	N/A	1/4 (25%)
<sup>1</sup> Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. <sup>2</sup> 43% indinavir, 42% nelfinavir, 10% ritonavir, 15% saquinavir. <sup>3</sup> 41% indinavir, 38% nelfinavir, 4% ritonavir, 16% saquinavir. <sup>4</sup> 86% indinavir, 54% nelfinavir, 80% ritonavir, 70% saquinavir.			

Virologic response to lopinavir and ritonavir therapy with respect to phenotypic susceptibility to lopinavir at baseline was examined in Study 957. In this study 56 NNRTI-naïve patients with HIV-1 RNA >1,000 copies/mL despite previous therapy with at least two protease inhibitors selected from indinavir, nelfinavir, ritonavir, and saquinavir were randomized to receive one of two doses of lopinavir and ritonavir in combination with efavirenz and nucleoside reverse transcriptase inhibitors (NRTIs). The EC<sub>50</sub> values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold the wild-type EC<sub>50</sub> value. Fifty-five percent (31/56) of these baseline isolates displayed >4-fold reduced susceptibility to lopinavir. These 31 isolates had a median reduction in lopinavir susceptibility of 18-fold. Response to therapy by baseline lopinavir susceptibility is shown in Table 17.

**Table 17. HIV-1 RNA Response at Week 48 by Baseline Lopinavir Susceptibility<sup>1</sup>**

Lopinavir susceptibility <sup>2</sup> at baseline	HIV-1 RNA <400 copies/mL (%)	HIV-1 RNA <50 copies/mL (%)
< 10 fold	25/27 (93%)	22/27 (81%)
> 10 and < 40 fold	11/15 (73%)	9/15 (60%)
≥ 40 fold	2/8 (25%)	2/8 (25%)
1 Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic.		
2 Fold change in susceptibility from wild type.		

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

Lopinavir and ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6-2.2 times (mice) and 0.5 times (rats) the human exposure (based on AUC<sub>0-24hr</sub> measurement) at the recommended dose of 400/100 mg lopinavir and ritonavir twice daily. Administration of lopinavir and ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg lopinavir and ritonavir twice daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg lopinavir and ritonavir twice daily regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

#### Mutagenesis

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

### Impairment of Fertility

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily).

## **14 CLINICAL STUDIES**

### **14.1 Adult Patients without Prior Antiretroviral Therapy**

Study 863: Lopinavir and Ritonavir Capsules twice daily + stavudine + lamivudine compared to nelfinavir three times daily + stavudine + lamivudine

Study 863 was a randomized, double-blind, multicenter trial comparing treatment with lopinavir and ritonavir capsules (400/100 mg twice daily) plus stavudine and lamivudine versus nelfinavir (750 mg three times daily) plus stavudine and lamivudine in 653 antiretroviral treatment naïve patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4+ cell count was 259 cells/mm<sup>3</sup> (range: 2 to 949 cells/mm<sup>3</sup>) and mean baseline plasma HIV-1 RNA was 4.9 log<sub>10</sub> copies/mL (range: 2.6 to 6.8 log<sub>10</sub> copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 18.

**Table 18. Outcomes of Randomized Treatment Through Week 48 (Study 863)**

<b>Outcome</b>	<b>Lopinavir and Ritonavir +d4T+3TC (N = 326)</b>	<b>Nelfinavir+d4T+3TC (N = 327)</b>
Responder <sup>1</sup>	75%	62%
Virologic failure <sup>2</sup>	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse events	4%	4%
Discontinued for other reasons <sup>3</sup>	10%	8%
<sup>1</sup> Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48. <sup>2</sup> Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48. <sup>3</sup> Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through Week 48, including patients who discontinued subsequent to virologic failure, was 17% in the lopinavir and ritonavir arm and 24% in the nelfinavir arm.		

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the lopinavir and ritonavir arm compared to the nelfinavir arm with HIV-1 RNA < 400 copies/mL (75% vs. 62%, respectively) and HIV-1 RNA < 50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV-1 RNA level subgroups is presented in Table 19.

**Table 19. Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)**

Baseline Viral Load (HIV-1 RNA copies/mL)	Lopinavir and Ritonavir +d4T+3TC			Nelfinavir +d4T+3TC		
	<400 copies/mL <sup>1</sup>	<50 copies/mL <sup>2</sup>	n	<400 copies/mL <sup>1</sup>	<50 copies/mL <sup>2</sup>	n
< 30,000	74%	71%	82	79%	72%	87
≥ 30,000 to < 100,000	81%	73%	79	67%	54%	79
≥ 100,000 to < 250,000	75%	64%	83	60%	47%	72
≥ 250,000	72%	60%	82	44%	33%	89
1 Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.						
2 Patients achieved HIV-1 RNA < 50 copies/mL at Week 48.						

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

Study 730: Lopinavir and Ritonavir Tablets once daily + tenofovir DF + emtricitabine compared to Lopinavir and Ritonavir Tablets twice daily + tenofovir DF + emtricitabine

Study 730 was a randomized, open-label, multicenter trial comparing treatment with lopinavir and ritonavir 800/200 mg once daily plus tenofovir DF and emtricitabine versus lopinavir and ritonavir 400/100 mg twice daily plus tenofovir DF and emtricitabine in 664 antiretroviral treatment-naïve patients. Patients were randomized in a 1:1 ratio to receive either lopinavir and ritonavir 800/200 mg once daily (n = 333) or lopinavir and ritonavir 400/100 mg twice daily (n = 331). Further stratification within each group was 1:1 (tablet vs. capsule). Patients administered the capsule were switched to the tablet formulation at Week 8 and maintained on their randomized dosing schedule. Patients were administered emtricitabine 200 mg once daily and tenofovir DF 300 mg once daily. Mean age of patients enrolled was 39 years (range: 19 to 71); 75% were Caucasian, and 78% were male. Mean baseline CD4+ cell count was 216 cells/mm<sup>3</sup> (range: 20 to 775 cells/mm<sup>3</sup>) and mean baseline plasma HIV-1 RNA was 5.0 log<sub>10</sub> copies/mL (range: 1.7 to 7.0 log<sub>10</sub> copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 20.

**Table 20. Outcomes of Randomized Treatment Through Week 48 (Study 730)**

Outcome	Lopinavir and Ritonavir Once Daily + TDF + FTC (n = 333)	Lopinavir and Ritonavir Twice Daily + TDF + FTC (n = 331)
Responder <sup>1</sup>	78%	77%
Virologic failure <sup>2</sup>	10%	8%
Rebound	5%	5%
Never suppressed through Week 48	5%	3%
Death	1%	<1%
Discontinued due to adverse events	4%	3%
Discontinued for other reasons <sup>3</sup>	8%	11%
<sup>1</sup> Patients achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48. <sup>2</sup> Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48. <sup>3</sup> Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.		

Through 48 weeks of therapy, 78% in the lopinavir and ritonavir once daily arm and 77% in the lopinavir and ritonavir twice daily arm achieved and maintained HIV-1 RNA < 50 copies/mL (95% confidence interval for the difference, -5.9% to 6.8%). Mean CD4+ cell count increases at Week 48 were 186 cells/mm<sup>3</sup> for the lopinavir and ritonavir once daily arm and 198 cells/mm<sup>3</sup> for the lopinavir and ritonavir twice daily arm.

## 14.2 Adult Patients with Prior Antiretroviral Therapy

Study 888: Lopinavir and Ritonavir Capsules twice daily + nevirapine + NRTIs compared to investigator-selected protease inhibitor(s) + nevirapine + NRTIs

Study 888 was a randomized, open-label, multicenter trial comparing treatment with lopinavir and ritonavir capsules (400/100 mg twice daily) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naïve patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD4+ cell count was 322 cells/mm<sup>3</sup> (range: 10 to 1059 cells/mm<sup>3</sup>) and mean baseline plasma HIV-1 RNA was 4.1 log<sub>10</sub> copies/mL (range: 2.6 to 6.0 log<sub>10</sub> copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in [Table 21](#).

**Table 21. Outcomes of Randomized Treatment Through Week 48 (Study 888)**

<b>Outcome</b>	<b>Lopinavir and Ritonavir + nevirapine + NRTIs (n = 148)</b>	<b>Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n = 140)</b>
Responder <sup>1</sup>	57%	33%
Virologic failure <sup>2</sup>	24%	41%
Rebound	11%	19%
Never suppressed through Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons <sup>3</sup>	14%	13%
<sup>1</sup> Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48. <sup>2</sup> Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48. <sup>3</sup> Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.		

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the lopinavir and ritonavir arm compared to the investigator-selected protease inhibitor(s) arm with HIV-1 RNA < 400 copies/mL (57% vs. 33%, respectively).

Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 111 cells/mm<sup>3</sup> for the lopinavir and ritonavir arm and 112 cells/mm<sup>3</sup> for the investigator-selected protease inhibitor(s) arm.

Study 802: Lopinavir and Ritonavir Tablets 800/200 mg Once Daily Versus 400/100 mg Twice Daily when Co-administered with Nucleoside/Nucleotide Reverse Transcriptase Inhibitors in Antiretroviral-Experienced, HIV-1 Infected Subjects

M06-802 was a randomized open-label study comparing the safety, tolerability, and antiviral activity of once daily and twice daily dosing of lopinavir and ritonavir tablets in 599 subjects with detectable viral loads while receiving their current antiviral therapy. Of the enrolled subjects, 55% on both treatment arms had not been previously treated with a protease inhibitor and 81 – 88% had received prior NNRTIs as part of their anti-HIV treatment regimen. Patients were randomized in a 1:1 ratio to receive either lopinavir and ritonavir 800/200 mg once daily (n = 300) or lopinavir and ritonavir 400/100 mg twice daily (n = 299). Patients were administered at least two nucleoside/nucleotide reverse transcriptase inhibitors selected by the investigator. Mean age of patients enrolled was 41 years (range: 21 to 73); 51% were Caucasian, and 66% were male. Mean baseline CD4+ cell count was 254 cells/mm<sup>3</sup> (range: 4 to 952 cells/mm<sup>3</sup>) and mean baseline plasma HIV-1 RNA was 4.3 log<sub>10</sub> copies/mL (range: 1.7 to 6.6 log<sub>10</sub> copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 22.

**Table 22. Outcomes of Randomized Treatment Through Week 48 (Study 802)**

Outcome	Lopinavir and Ritonavir Once Daily + NRTIs (n = 300)	Lopinavir and Ritonavir Twice Daily + NRTIs (n = 299)
Virologic Success (HIV-1 RNA <50 copies/mL)	57%	54%
Virologic failure <sup>1</sup>	22%	24%
No virologic data in Week 48 window		
Discontinued study due to adverse event or death <sup>2</sup>	5%	7%
Discontinued study for other reasons <sup>3</sup>	13%	12%
Missing data during window but on study	3%	3%
<sup>1</sup> Includes patients who discontinued prior to Week 48 for lack or loss of efficacy and patients with HIV-1 RNA ≥ 50 copies/mL at Week 48. <sup>2</sup> Includes patients who discontinued due to adverse events or death at any time from Day 1 through Week 48 if this resulted in no virologic data on treatment at Week 48. <sup>3</sup> Includes withdrawal of consent, loss to follow-up, non-compliance, protocol violation and other reasons.		

Through 48 weeks of treatment, the mean change from baseline for CD4 + cell count was 135 cells/mm<sup>3</sup> for the once daily group and 122 cells/mm<sup>3</sup> for the twice daily group.

### 14.3 Other Studies Supporting Approval in Adult Patients

Study 720: Lopinavir and Ritonavir twice daily + stavudine + lamivudine

Study 765: Lopinavir and Ritonavir twice daily + nevirapine + NRTIs

Study 720 (patients without prior antiretroviral therapy) and study 765 (patients with prior protease inhibitor therapy) were randomized, blinded, multi-center trials evaluating treatment with lopinavir and ritonavir at up to three dose levels (200/100 mg twice daily [720 only], 400/100 mg twice daily, and 400/200 mg twice daily). In Study 720, all patients switched to 400/100 mg twice daily between Weeks 48-72. Patients in study 720 had a mean age of 35 years, 70% were Caucasian, and 96% were male, while patients in study 765 had a mean age of 40 years, 73% were Caucasian, and 90% were male. Mean (range) baseline CD4+ cell counts for patients in study 720 and study 765 were 338 (3-918) and 372 (72-807) cells/mm<sup>3</sup>, respectively. Mean (range) baseline plasma HIV-1 RNA levels for patients in study 720 and study 765 were 4.9 (3.3 to 6.3) and 4.0 (2.9 to 5.8) log<sub>10</sub> copies/mL, respectively.



Through 360 weeks of treatment in study 720, the proportion of patients with HIV-1 RNA < 400 (< 50) copies/mL was 61% (59%) [n = 100]. Among patients completing 360 weeks of treatment with CD4+ cell count measurements [n=60], the mean (median) increase in CD4+ cell count was 501 (457) cells/mm<sup>3</sup>. Thirty-nine patients (39%) discontinued the study, including 13 (13%) discontinuations due to adverse reactions and 1 (1%) death.

Through 144 weeks of treatment in study 765, the proportion of patients with HIV-1 RNA < 400 (< 50) copies/mL was 54% (50%) [n = 70], and the corresponding mean increase in CD4+ cell count was 212 cells/mm<sup>3</sup>. Twenty-seven patients (39%) discontinued the study, including 5 (7%) discontinuations secondary to adverse reactions and 2 (3%) deaths.

#### **14.4 Pediatric Studies**

Study 1030 was an open-label, multicenter, dose-finding trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of lopinavir and ritonavir oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of 300/75 mg/m<sup>2</sup> twice daily plus 2 NRTIs in HIV-1 infected infants ≥14 days and <6 months of age.

Ten infants, ≥14 days and <6 wks of age, were enrolled at a median (range) age of 5.7 (3.6-6.0) weeks and all completed 24 weeks. At entry, median (range) HIV-1 RNA was 6.0 (4.7-7.2) log<sub>10</sub> copies/mL. Seven of 10 infants had HIV-1 RNA <400 copies/mL at Week 24. At entry, median (range) CD4+ percentage was 41 (16-59) with a median decrease of 1% (95% CI: -10, 18) from baseline to week 24 in 6 infants with available data.

Twenty-one infants, between 6 weeks and 6 months of age, were enrolled at a median (range) age of 14.7 (6.9-25.7) weeks and 19 of 21 infants completed 24 weeks. At entry, median (range) HIV RNA level was 5.8 (3.7-6.9) log<sub>10</sub> copies/mL. Ten of 21 infants had HIV RNA <400 copies/mL at Week 24. At entry, the median (range) CD4+ percentage was 32 (11-54) with a median increase of 4% (95% CI: -1, 9) from baseline to week 24 in 19 infants with available data.

*See Clinical Pharmacology (12.3) for pharmacokinetic results.*

Study 940 was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of lopinavir and ritonavir oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naïve (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m<sup>2</sup> or 300 mg lopinavir/75 mg ritonavir per m<sup>2</sup>. Naïve patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m<sup>2</sup> dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD4+ cell count was 838 cells/mm<sup>3</sup> and mean baseline plasma HIV-1 RNA was 4.7 log<sub>10</sub> copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV-1 RNA < 400 copies/mL was 80% for antiretroviral naïve patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD4+ cell count was 404 cells/mm<sup>3</sup> for antiretroviral naïve and 284 cells/mm<sup>3</sup> for antiretroviral experienced patients treated through 48 weeks. At 48 weeks, two patients (2%) had prematurely discontinued the study. One antiretroviral naïve patient prematurely discontinued secondary to an adverse reaction, while one antiretroviral experienced patient prematurely discontinued secondary to an HIV-1 related event.

Dose selection in pediatric patients was based on the following:

- Among patients 14 days to 6 months of age receiving 300/75 mg/m<sup>2</sup> twice daily without nevirapine, plasma concentrations were lower than those observed in adults or in older children. This dose resulted in HIV-1 RNA < 400 copies/mL in 55% of patients (70% in those initiating treatment at <6 weeks of age).
- Among patients 6 months to 12 years of age, the 230/57.5 mg/m<sup>2</sup> oral solution twice daily regimen without nevirapine and the 300/75 mg/m<sup>2</sup> oral solution twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine). These doses resulted in treatment benefit (proportion of patients with HIV-1 RNA < 400 copies/mL) similar to that seen in the adult clinical trials.

- Among patients 12 to 18 years of age receiving 400/100 mg/m<sup>2</sup> or 480/120 mg/m<sup>2</sup> (with efavirenz) twice daily, plasma concentrations were 60-100% higher than among 6 to 12 year old patients receiving 230/57.5 mg/m<sup>2</sup>. Mean apparent clearance was similar to that observed in adult patients receiving standard dose and in patients 6 to 12 years of age. Although changes in HIV-1 RNA in patients with prior treatment failure were less than anticipated, the pharmacokinetic data supports use of similar dosing as in patients 6 to 12 years of age, not to exceed the recommended adult dose.
- For all age groups, the body surface area dosing was converted to body weight dosing using the patient's prescribed lopinavir dose.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Lopinavir and Ritonavir Oral Solution USP is a colorless to yellow colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir and 100 mg ritonavir per 5 mL (80 mg lopinavir and 20 mg ritonavir per mL) packaged with a marked syringe and bottle adapter in the following size:

160 mL bottle ..... (NDC 0527-1947-48)

### Recommended Storage

Store lopinavir and ritonavir oral solution at 2°-8°C (36°-46°F) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated lopinavir and ritonavir oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 25°C (77°F), oral solution should be used within 2 months.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling ([Medication Guide](#))

Patients or parents of patients should be informed that:

### *General Information*

- They should pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or underdose of lopinavir and ritonavir.
- They should inform their healthcare provider if their children's weight changes in order to make sure that the child's lopinavir and ritonavir dose is the correct one.
- They should take the prescribed dose of lopinavir and ritonavir as directed and to set up a daily routine in order to do so.

- Lopinavir and ritonavir oral solution should be taken with food to enhance absorption.
- Sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using lopinavir and ritonavir. Patients should be advised to take lopinavir and ritonavir and other concomitant antiretroviral therapy every day as prescribed. Lopinavir and ritonavir must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of lopinavir and ritonavir is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose. The amount of HIV-1 virus in their blood may increase if the medicine is stopped for even a short time. The virus may become resistant to lopinavir and ritonavir and become harder to treat.
- Lopinavir and ritonavir is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using lopinavir and ritonavir.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

#### *Drug Interactions*

- Lopinavir and ritonavir may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's Wort.
- Patients taking didanosine should take didanosine one hour before or two hours after lopinavir and ritonavir oral solution.

- If they are receiving avanafil, sildenafil, tadalafil, or vardenafil for the treatment of erectile dysfunction, there may be an increased risk of associated adverse reactions including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor. If they are currently using or planning to use avanafil or tadalafil (for the treatment of pulmonary arterial hypertension) they should ask their doctor about potential adverse reactions these medications may cause when taken with lopinavir and ritonavir. The doctor may choose not to keep them on avanafil, or may adjust the dose of tadalafil while initiating treatment with lopinavir and ritonavir.
- If they are receiving estrogen-based hormonal contraceptives, additional or alternate contraceptive measures should be used during therapy with lopinavir and ritonavir.
- If they are taking or before they begin using Serevent<sup>®</sup> (salmeterol) and lopinavir and ritonavir, they should talk to their doctor about problems these two medications may cause when taken together. The doctor may choose not to keep someone on Serevent<sup>®</sup> (salmeterol).
- If they are taking or before they begin taking Advair<sup>®</sup> (salmeterol in combination with fluticasone propionate) and lopinavir and ritonavir, they should talk to their doctor about problems these two medications may cause when taken together. The doctor may choose not to keep someone on Advair<sup>®</sup> (salmeterol in combination with fluticasone propionate).

#### *Potential Adverse Effects*

- Skin rashes ranging in severity from mild to toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, erythema multiforme, urticaria, and angioedema have been reported in patients receiving lopinavir and ritonavir or its components lopinavir and/or ritonavir. Patients should be advised to contact their healthcare provider if they develop a rash while taking lopinavir and ritonavir. The healthcare provider will determine if treatment should be continued or an alternative antiretroviral regimen used.

- Patients should be advised that appropriate liver function testing will be conducted prior to initiating and during therapy with lopinavir and ritonavir. Pre-existing liver disease including Hepatitis B or C can worsen with use of lopinavir and ritonavir. This can be seen as worsening of transaminase elevations or hepatic decompensation. Patients should be advised that their liver function tests will need to be monitored closely especially during the first several months of lopinavir and ritonavir treatment and that they should notify their healthcare provider if they develop the signs and symptoms of worsening liver disease including loss of appetite, abdominal pain, jaundice, and itchy skin.
- New onset of diabetes or exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during lopinavir and ritonavir use. Patients should be advised to notify their healthcare provider if they develop the signs and symptoms of diabetes mellitus including frequent urination, excessive thirst, extreme hunger or unusual weight loss and/or an increased blood sugar while on lopinavir and ritonavir as they may require a change in their diabetes treatment or new treatment.
- Lopinavir and ritonavir might produce changes in the electrocardiogram (e.g., PR and/or QT prolongation). Patients should consult their physician if they experience symptoms such as dizziness, lightheadedness, abnormal heart rhythm or loss of consciousness.
- They should seek medical assistance immediately if they develop a sustained penile erection lasting more than 4 hours while taking lopinavir and ritonavir and a PDE 5 Inhibitor such as Viagra, Cialis or Levitra.
- Redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.
- Patients should be informed that there may be a greater chance of developing diarrhea with the once daily regimen as compared with the twice daily regimen.

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## MEDICATION GUIDE

### **Lopinavir and Ritonavir** (loe pin' a veer) (ri toe' na veer) **Oral Solution USP**

Read this Medication Guide before you start taking lopinavir and ritonavir and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. You and your doctor should talk about your treatment with lopinavir and ritonavir before you start taking it and at regular check-ups. You should stay under your doctor's care when taking lopinavir and ritonavir.

#### **What is the most important information I should know about lopinavir and ritonavir?**

##### **Lopinavir and ritonavir may cause serious side effects, including:**

- **Interactions with other medicines. It is important to know the medicines that should not be taken with lopinavir and ritonavir.** For more information, see "[Who should not take lopinavir and ritonavir?](#)"
- **Changes in your heart rhythm and the electrical activity of your heart.** These changes may be seen on an EKG (electrocardiogram) and can lead to serious heart problems. Your risk for these problems may be higher if you:
  - already have a history of abnormal heart rhythm or other types of heart disease.
  - take other medicines that can affect your heart rhythm while you take lopinavir and ritonavir.

Tell your doctor right away if you have any of these symptoms while taking lopinavir and ritonavir:

- dizziness
- lightheadedness
- fainting
- sensation of abnormal heartbeats

See "[What are the possible side effects of lopinavir and ritonavir?](#)" for more information about serious side effects.

#### **What is lopinavir and ritonavir?**

Lopinavir and ritonavir is a prescription HIV-1 medicine that is used with other HIV medicines to treat HIV-1 (Human Immunodeficiency Virus) infection in adults and children 14 days of age and older. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). Lopinavir and ritonavir is a type of HIV medicine called a protease inhibitor. Lopinavir and ritonavir contains two medicines: lopinavir and ritonavir.

When used with other HIV medicines, lopinavir and ritonavir may help to reduce the amount of HIV in your blood (called “viral load”). Lopinavir and ritonavir may also help to increase the number of white blood cells called CD4 (T) cell which help fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

It is not known if lopinavir and ritonavir is safe and effective in children under 14 days old.

**Lopinavir and ritonavir does not cure HIV infection or AIDS.** People taking lopinavir and ritonavir may develop infections or other conditions associated with HIV infection, including opportunistic infections (for example, pneumonia and herpes virus infections).

Avoid doing things that can spread HIV-1 infection to others:

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

### **Who should not take lopinavir and ritonavir?**

#### **Do not take lopinavir and ritonavir if you take any of the following medicines:**

- alfuzosin (Uroxatral<sup>®</sup>)
- cisapride (Propulsid<sup>®</sup>, Quicksolv<sup>®</sup>)
- colchicine (Colcrys<sup>®</sup>), if you have kidney and/or liver problems
- dronedarone (Multaq<sup>®</sup>)
- elbasvir/grazoprevir (Zepatier<sup>®</sup>)
- ergot containing medicines including
  - ergotamine tartrate (Cafergot<sup>®</sup>, Migergot<sup>®</sup>, Ergomar<sup>®</sup>, Ergostat<sup>®</sup>, Medihaler<sup>®</sup>, Ergotamine, Wigraine<sup>®</sup>, Wigrettes<sup>®</sup>)
  - dihydroergotamine mesylate (D.H.E. 45<sup>®</sup>, Migranal<sup>®</sup>)
  - methylergonovine (Methergine<sup>®</sup>)
- lovastatin (Advicor<sup>®</sup>, Altoprev<sup>®</sup>, Mevacor<sup>®</sup>)
- midazolam oral syrup
- lurasidone (Latuda<sup>®</sup>), pimozide (Orap<sup>®</sup>)
- rifampin (Rifadin<sup>®</sup>, Rifamate<sup>®</sup>, Rifater<sup>®</sup>, Rimactane<sup>®</sup>)
- sildenafil (Revatio<sup>®</sup>), when used for the treatment of pulmonary arterial hypertension
- simvastatin (Zocor<sup>®</sup>, Vytorin<sup>®</sup>, Simcor<sup>®</sup>)
- St. John’s Wort (Hypericum perforatum)

- triazolam (Halcion<sup>®</sup>)

Serious problems can happen if you or your child take any of the medicines listed above with lopinavir and ritonavir.

- **Do not take lopinavir and ritonavir if you are allergic** to lopinavir, ritonavir or any of the ingredients in lopinavir and ritonavir. See the end of this Medication Guide for a complete list of ingredients in lopinavir and ritonavir.

### **What should I tell my doctor before taking lopinavir and ritonavir?**

**Lopinavir and ritonavir may not be right for you. Tell your doctor about all your medical conditions, including if you:**

- have any heart problems, including if you have a condition called Congenital Long QT Syndrome.
- have or had pancreas problems.
- have liver problems, including Hepatitis B or Hepatitis C.
- have diabetes.
- have hemophilia. People who take lopinavir and ritonavir may have increased bleeding.
- have low potassium in your blood.
- are pregnant or plan to become pregnant. Taking lopinavir and ritonavir during pregnancy has not been associated with an increased risk of birth defects. You and your doctor should decide if lopinavir and ritonavir is right for you.

**Pregnancy Registry.** There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of the pregnancy registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take lopinavir and ritonavir.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - Talk to your doctor about the best way to feed your baby.

**Tell your doctor about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Many medicines interact with lopinavir and ritonavir. Do not start taking a new medicine without telling your doctor or pharmacist. Your doctor can tell you if it is safe to take lopinavir and ritonavir with other medicines. Your doctor may need to change the dose of other medicines while you take lopinavir and ritonavir.

Especially tell your doctor if you take:

- medicine to treat HIV
- estrogen-based contraceptives (birth control pills and patches). Lopinavir and ritonavir may reduce the effectiveness of estrogen-based contraceptives. During treatment with lopinavir and ritonavir, you should use a different type or an extra form of birth control. Talk to your doctor about what types of birth control you can use to prevent pregnancy while taking lopinavir and ritonavir.
- medicines to prevent organ transplant rejection
- medicines to treat cancer
- amiodarone (Cordarone<sup>®</sup>, Pacerone<sup>®</sup>)
- atorvastatin (Lipitor<sup>®</sup>)
- atovaquone (Marlarone<sup>®</sup>, Mepron<sup>®</sup>)
- avanafil (Stendra<sup>®</sup>), sildenafil (Viagra<sup>®</sup>), tadalafil (Cialis<sup>®</sup>), or vardenafil (Levitra<sup>®</sup>) for the treatment of erectile dysfunction (ED). If you get dizzy or faint (low blood pressure), have vision changes or have an erection that last longer than 4 hours, call your doctor or get medical help right away.
- bedaquiline (Sirturo<sup>®</sup>)
- bepridil (Bepadin<sup>®</sup>, Vascor<sup>®</sup>)
- boceprevir (Victrelis<sup>®</sup>)
- bosentan (Tracleer<sup>®</sup>)
- budesonide (Rhinocort<sup>®</sup>, Symbicort<sup>®</sup>, Pulmicort<sup>®</sup>, Entocort EC<sup>®</sup>)
- bupropion (Aplenzin<sup>®</sup>, Forfivo XL<sup>®</sup>, Wellbutrin<sup>®</sup>, Zyban<sup>®</sup>)
- carbamazepine (Carbatrol<sup>®</sup>, Epitol<sup>®</sup>, Equetro<sup>®</sup>, Tegretol<sup>®</sup>)
- clarithromycin (Biaxin<sup>®</sup>, Prevpac<sup>®</sup>)
- colchicine (Colcrys<sup>®</sup>)
- dexamethasone (Maxidex<sup>®</sup>, Ozurdex<sup>®</sup>)
- disulfiram
- felodipine
- fentanyl (Abstral<sup>®</sup>, Actiq<sup>®</sup>, Duragesic<sup>®</sup>, Fentora<sup>®</sup>, Lazanda<sup>®</sup>, Onsolis<sup>®</sup>, Subsys<sup>®</sup>)
- fluticasone (Cutivate<sup>®</sup>, Flonase<sup>®</sup>, Flovent<sup>®</sup>, Flovent Diskus<sup>®</sup>, Flovent HFA<sup>®</sup>, Veramyst<sup>®</sup>)
- itraconazole (Onmel<sup>®</sup>, Sporanox<sup>®</sup>)
- isavuconazonium (Cresemba<sup>®</sup>)
- ketoconazole (Extina<sup>®</sup>, Ketozone<sup>®</sup>, Nizoral<sup>®</sup>, Xolegel<sup>®</sup>)
- lamotrigine (Lamictal<sup>®</sup>)
- lidocaine
- methadone hydrochloride (Dolphine hydrochloride, Methadose<sup>®</sup>)
- metronidazole
- nicardipine (Cardene<sup>®</sup>)
- nifedipine (Adalat CC<sup>®</sup>, Afeditab CR<sup>®</sup>, Procardia<sup>®</sup>)
- ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak<sup>®</sup>)
- phenobarbital
- phenytoin (Dilantin<sup>®</sup>, Phenytek<sup>®</sup>)
- prednisone
- quinidine (Quinidex<sup>®</sup>)
- quetiapine (Seroquel<sup>®</sup>)
- rifabutin (Mycobutin<sup>®</sup>)
- rivaroxaban (Xarelto<sup>®</sup>)

- rosuvastatin (Crestor<sup>®</sup>)
- salmeterol (Serevent<sup>®</sup>) or salmeterol when taken in combination with fluticasone (Advair Diskus<sup>®</sup>, Advair HFA<sup>®</sup>)
- simeprevir (Olysio<sup>®</sup>)
- tadalafil (Adcirca<sup>®</sup>) for the treatment of pulmonary arterial hypertension
- trazodone (Oleptro<sup>®</sup>)
- valproate (Depakote<sup>®</sup>, Depakene<sup>®</sup>, Depacon<sup>®</sup>)
- voriconazole (Vfend<sup>®</sup>)
- warfarin (Coumadin<sup>®</sup>, Jantoven<sup>®</sup>)

Lopinavir and ritonavir should not be administered once daily in combination with carbamazepine (Carbatrol<sup>®</sup>, Epitol<sup>®</sup>, Equetro<sup>®</sup>, Tegretol<sup>®</sup>), phenobarbital, or phenytoin (Dilantin<sup>®</sup>, Phenytek<sup>®</sup>).

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Know all the medicines that you take. Keep a list of them with you to show doctors and pharmacists when you get a new medicine.

**If you are not sure if you are taking a medicine above, ask your doctor.**

#### **How should I take lopinavir and ritonavir?**

- Take lopinavir and ritonavir every day exactly as prescribed by your doctor.
- It is very important to set up a dosing schedule and follow it every day.
- Do not change your treatment or stop treatment without first talking with your doctor.
- You **should not** take lopinavir and ritonavir oral solution if you are pregnant.
- If you are taking both didanosine (Videx<sup>®</sup>) and lopinavir and ritonavir:
  - take didanosine either one hour before or two hours after taking lopinavir and ritonavir oral solution.
- Do not miss a dose of lopinavir and ritonavir. This could make the virus harder to treat. If you forget to take lopinavir and ritonavir, take the missed dose right away. If it is almost time for your next dose, do not take the missed dose. Instead, follow your regular dosing schedule by taking your next dose at its regular time. Do not take more than one dose of lopinavir and ritonavir at one time.
- If you take more than the prescribed dose of lopinavir and ritonavir, call your doctor or go to the nearest emergency room right away.
- Take lopinavir and ritonavir oral solution with food to help it work better.
- If your child is prescribed lopinavir and ritonavir, tell your doctor if your child's weight changes.
- Lopinavir and ritonavir **should not** be given one time each day in children. When giving lopinavir and ritonavir to your child, give lopinavir and ritonavir exactly as prescribed.

- Lopinavir and ritonavir oral solution contains propylene glycol and a large amount of alcohol. Lopinavir and ritonavir oral solution **should not** be given to babies younger than 14 days of age unless your doctor thinks it is right for your baby.
  - If a young child drinks more than the recommended dose, it could make them sick. Contact your local poison control center or emergency room right away.
  - Talk with your doctor if you take or plan to take metronidazole or disulfiram. You can have severe nausea and vomiting if you take these medicines with lopinavir and ritonavir.
- When your lopinavir and ritonavir supply starts to run low, get more from your doctor or pharmacy. It is important not to run out of lopinavir and ritonavir. The amount of HIV-1 virus in your blood may increase if the medicine is stopped for even a short time. The virus may become resistant to lopinavir and ritonavir and become harder to treat.

### What are the possible side effects of lopinavir and ritonavir?

#### Lopinavir and ritonavir can cause serious side effects, including:

- See [“What is the most important information I should know about lopinavir and ritonavir?”](#)
- **Inflammation of the pancreas (pancreatitis).** Some people who take lopinavir and ritonavir get inflammation of the pancreas which may be serious and cause death. You have a higher chance of getting pancreatitis if you have had it before. Tell your doctor if you have nausea, vomiting, or abdominal pain while taking lopinavir and ritonavir. These may be signs of pancreatitis.
- **Liver problems.** Liver problems, including death, can happen in people who take lopinavir and ritonavir. Your doctor should do blood tests before and during your treatment with lopinavir and ritonavir to check your liver function. Some people with liver disease such as Hepatitis B and Hepatitis C who take lopinavir and ritonavir may have worsening liver disease. Tell your doctor right away if you have any of these signs and symptoms of liver problems:
  - loss of appetite
  - yellow skin and whites of eyes (jaundice)
  - dark-colored urine
  - pale colored stools
  - itchy skin
  - stomach area (abdominal) pain
- **Diabetes and high blood sugar (hyperglycemia).** Some people who take protease inhibitors including lopinavir and ritonavir get new or more serious diabetes, or high blood sugar. Tell your doctor if you notice an increase in thirst or urinate often while taking lopinavir and ritonavir.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Call your doctor right away if you start having new symptoms after starting your HIV medicine.

- **Increases in certain fat (triglycerides and cholesterol) levels in your blood.** Large increases of triglycerides and cholesterol can be seen in blood test results of some people who take lopinavir and ritonavir. Your doctor should do blood tests to check your cholesterol and triglyceride levels before you start taking lopinavir and ritonavir and during your treatment.
- **Changes in body fat.** Changes in body fat in some people who take antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.
- **Increased bleeding for hemophiliacs.** Some people with hemophilia have increased bleeding with protease inhibitors including lopinavir and ritonavir.
- **Allergic reactions.** Skin rashes, some of them severe, can occur in people who take lopinavir and ritonavir. Tell your doctor if you had a rash when you took another medicine for your HIV-1 infection or if you notice any skin rash when you take lopinavir and ritonavir.
- **Babies taking lopinavir and ritonavir oral solution may have side effects.** Lopinavir and ritonavir oral solution contains alcohol and propylene glycol. Call your doctor right away if your baby appears too sleepy or their breathing has changed.

Common side effects of lopinavir and ritonavir include:

- diarrhea
- nausea
- increased fats in blood (triglycerides or cholesterol)
- vomiting

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all of the possible side effects of lopinavir and ritonavir. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store lopinavir and ritonavir?**

#### **Lopinavir and ritonavir oral solution:**

- Store lopinavir and ritonavir oral solution in a refrigerator, between 36°F to 46°F (2°C to 8°C). Lopinavir and ritonavir oral solution that is kept refrigerated may be used until the expiration date printed on the label.
- Lopinavir and ritonavir oral solution that is stored at room temperature (less than 77°F or 25°C) should be used within 2 months.
- Keep lopinavir and ritonavir away from high heat.

Throw away any medicine that is out of date or that you no longer need.

**Keep lopinavir and ritonavir and all medicines out of the reach of children.**



### **General information about lopinavir and ritonavir**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lopinavir and ritonavir for a condition for which it was not prescribed. Do not give lopinavir and ritonavir to other people, even if they have the same condition you have. It may harm them.

This Medication Guide summarizes the most important information about lopinavir and ritonavir. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about lopinavir and ritonavir that is written for health professionals.

### **What are the ingredients in lopinavir and ritonavir?**

Active ingredients: lopinavir and ritonavir

Inactive ingredients:

**Lopinavir and ritonavir oral solution:** alcohol, bubble gum flavor, glycerin, high fructose corn syrup, malic acid, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, sodium hydroxide, sucralose, and water.

**Lopinavir and ritonavir oral solution contains 42.4% alcohol (v/v).** See **“How should I take lopinavir and ritonavir?”**

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**INSTRUCTIONS FOR USE**  
**Lopinavir and Ritonavir**  
**(loe pin' a veer) (ri toe' na veer)**  
**Oral Solution USP**

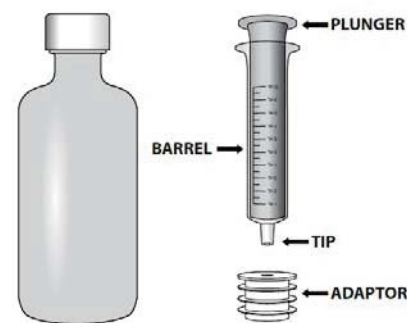
Read this Instructions for Use before you start taking lopinavir and ritonavir oral solution and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment.

**Important information about measuring lopinavir and ritonavir oral solution:**

Always use the oral syringe that comes with your lopinavir and ritonavir oral solution to measure your prescribed dose. Ask your doctor or pharmacist to show you how to measure your prescribed dose.

Each lopinavir and ritonavir oral solution carton contains:

- 1 Lopinavir and Ritonavir Oral Solution bottle
- 1 Bottle adapter
- 1 Oral syringe
- 1 Prescribing Information
- 1 Medication Guide and Instructions for Use

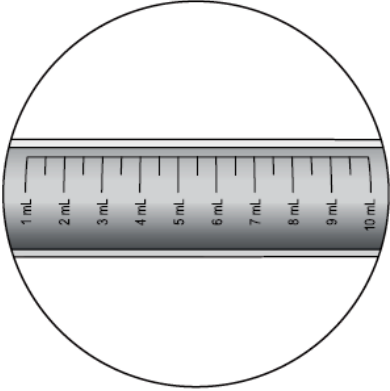

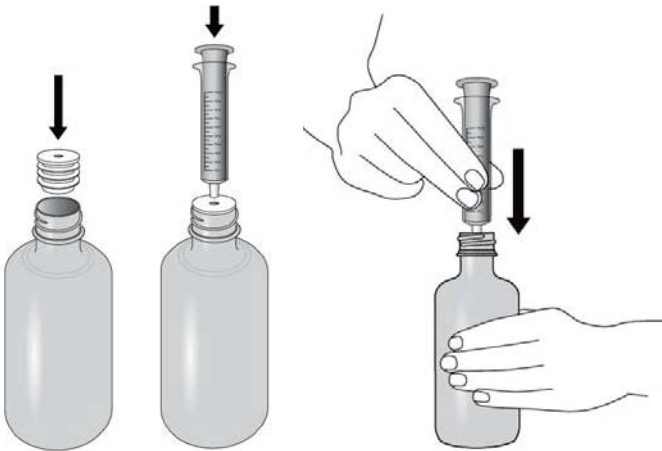


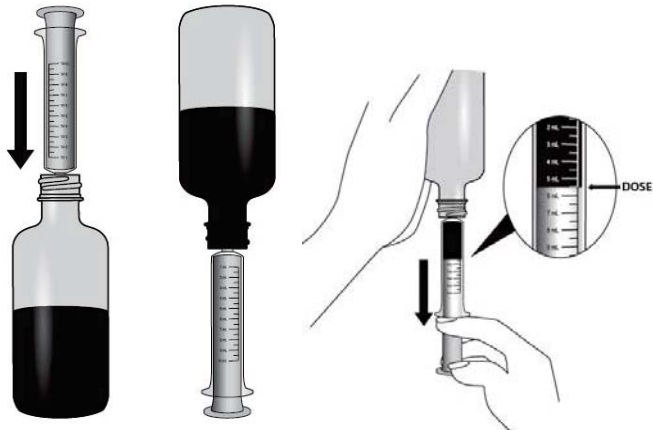
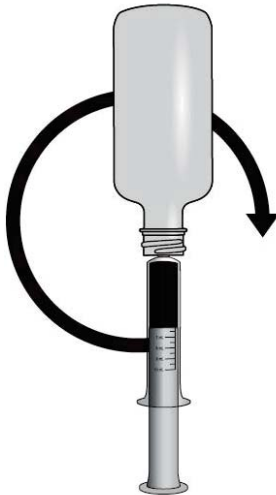
**Step 1:** Remove the lopinavir and ritonavir oral solution bottle, bottle adapter, and oral syringe from the carton.

**Step 2:** Open the bottle by pressing downward firmly on the child-resistant cap and twisting it in the direction of the arrow in the figure (counter-clockwise).

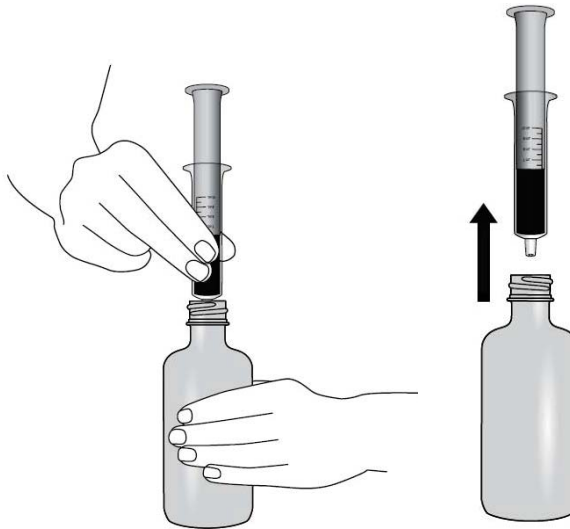
**Do not throw away the child-resistant cap.**



<p><b>Step 3:</b> Check the dose in milliliters (mL) as prescribed by your doctor. Find this number on the oral syringe.</p>	
<p><b>Step 4:</b> Push the oral syringe plunger to the bottom of the barrel of the oral syringe (toward its tip) to remove excess air.</p>	
<p><b>Step 5:</b> Remove bottle cap and insert bottle adapter into bottle opening.</p> <p>Insert the oral syringe tip into the upright bottle through the opening of the bottle adapter until it is firmly in place.</p>	

<p><b>Step 6:</b> With the oral syringe in place, turn the bottle upside down. Pull the plunger to withdraw the dose prescribed by your doctor (the amount of oral solution in Step 3).</p> <p>If you see air bubbles in the oral syringe, fully push the plunger so that the oral solution flows back into the bottle. Then withdraw your prescribed dose of oral solution.</p>	
<p><b>Step 7:</b> Leave the oral syringe in the bottle adapter and turn the bottle to an upright position.</p>	

**Step 8:** Place the bottle on a flat surface. Remove the oral syringe from the bottle adapter and bottle by pulling straight up on the oral syringe outer barrel.

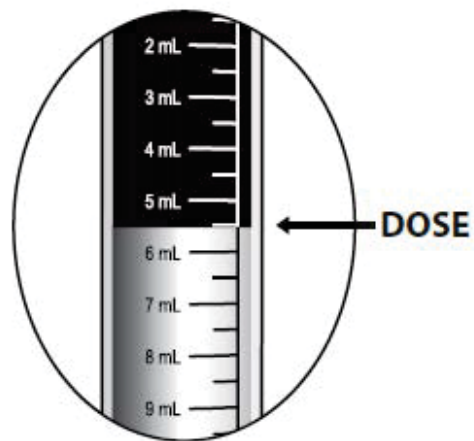


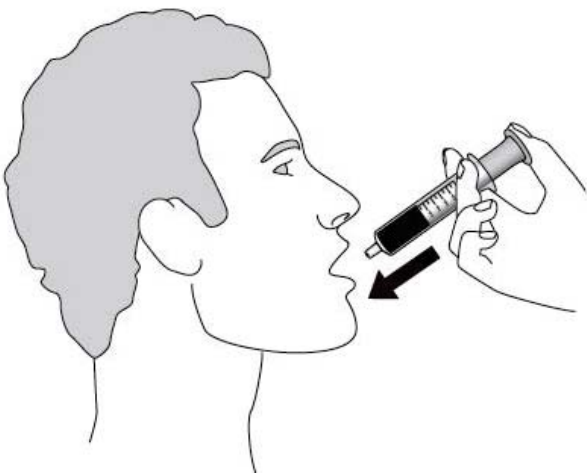
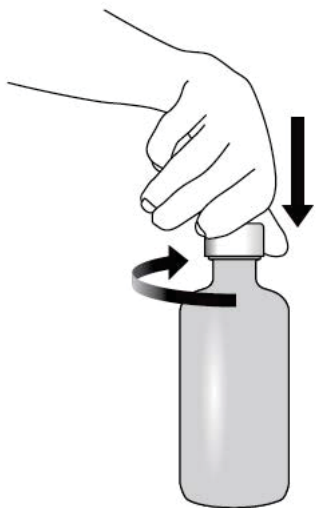
**Step 9:** Check that the correct dose was drawn up into the oral syringe.

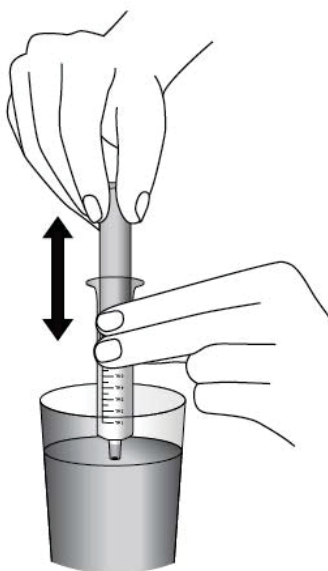
Measure the dosage from the base of the plunger.

If the dose is not correct, insert the oral syringe tip firmly into the bottle adapter. Fully push in the plunger so that the oral solution flows back into the bottle.

Repeat Steps 6 through 8, if required.



<p><b>Step 10:</b> Take the dose of lopinavir and ritonavir oral solution.</p> <ul style="list-style-type: none"><li>• Swallow the lopinavir and ritonavir oral solution directly from the oral syringe.</li><li>• Place the tip of the oral syringe in your mouth, pointed towards your cheek. Close your lips around the barrel of the oral syringe.</li><li>• Slowly push down the oral syringe plunger until the oral syringe is empty.</li></ul> <p>Note: There may be some medicine that remains in the tip of the oral syringe. No additional action is necessary to account for residual medication remaining in the tip.</p>	 A line drawing of a person's head in profile, facing right. An oral syringe is held in their mouth, with the tip pointing towards the cheek. A hand is shown pushing the plunger of the syringe. A black arrow points from the syringe tip into the mouth, indicating the direction of medication flow.
<p><b>Step 11:</b> Put the child-resistant cap back on the bottle. The cap will fit over the bottle adapter.</p>	 A line drawing of a hand placing a cap onto a bottle. The hand is shown from the side, with the thumb and index finger gripping the cap. A black arrow points down towards the cap, and a curved black arrow indicates the direction of rotation for the cap.

<p><b>Step 12:</b> Rinse the oral syringe with tap water after each use.</p> <ul style="list-style-type: none"><li>• Remove the plunger from the oral syringe barrel.</li><li>• Rinse the oral syringe barrel and plunger with water and let them air dry.</li><li>• When the oral syringe barrel and plunger are dry, put the plunger back into the oral syringe barrel for the next use.</li></ul> <p><b>Do not throw away the oral syringe.</b></p>	
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**How should I store lopinavir and ritonavir oral solution?**

- Store lopinavir and ritonavir oral solution in a refrigerator, between 36°F to 46°F (2°C to 8°C). Lopinavir and ritonavir oral solution that is kept refrigerated may be used until the expiration date printed on the label.
- Lopinavir and ritonavir oral solution that is stored at room temperature (less than 77°F or 25°C) should be used within 2 months.
- Keep lopinavir and ritonavir oral solution away from high heat.

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