AUROBINDO
P1523690
Lopinavir and Ritonavir Tablets USP

Item Code With Serial Number in 2D format to be printed at printer's end
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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use LOPINAVIR AND RITONAVIR TABLETS safely and effectively. See full prescribing information for LOPINAVIR AND RITONAVIR TABLETS.**

**LOPINAVIR and RITONAVIR tablet, for oral use**
**Initial U.S. Approval: 2000**

**----------RECENT MAJOR CHANGES----------**

Contraindications (4) 12/2019

**----------INDICATIONS AND USAGE----------**

Lopinavir and ritonavir tablets are 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----------**

Tablets: May be taken with or without food, swallowed whole and not chewed, broken, or crushed. (2.1)
Oral solution: must be taken with food. (2.1)

Adults (2.3):
- Total recommended daily dosage is 800/200 mg given once or twice daily.
- Lopinavir and ritonavir tablets can be given as once daily or twice daily regimen. See Full Prescribing Information for details.
- Lopinavir and ritonavir tablets 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. (2.5, 8.1, 12.3)

Pediatric Patients (14 days and older) (2.4):
- Lopinavir and ritonavir tablets 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 tablets may be needed when co-administering with efavirenz, nevirapine, or nelfinavir. (2.3, 2.4, 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 (2.4, 5.2)

Pregnancy (2.5):
- 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 tablets dose for pregnant patients with any documented lopinavir and ritonavir tablets-associated resistance substitutions.
- No dose adjustment of lopinavir and ritonavir tablets are required for patients during the postpartum period.

**----------DOSAGE FORMS AND STRENGTHS----------**

- Tablets: 200 mg lopinavir and 50 mg ritonavir (3)
- Tablets: 100 mg lopinavir and 25 mg ritonavir (3)

**----------CONTRAINDICATIONS----------**

- Hypersensitivity to lopinavir and ritonavir tablets (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 lifethreatening 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. (2.4, 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 Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or 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.**

**Issued: February 2020**

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**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

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

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

**2 DOSAGE AND ADMINISTRATION**

**2.1 General Administration Recommendations**

Lopinavir and ritonavir tablets may be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed. Lopinavir and ritonavir oral solution must be taken with food.

**2.3 Dosage Recommendations in Adults**

Lopinavir and ritonavir tablets can be given in once daily or twice daily dosing regimen at dosages noted in Tables 1 and 2. Lopinavir and ritonavir tablets 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 pediatric patients younger than 18 years of age *[see Dosage and Administration (2.4)]*.
- In pregnant women *[see Dosage and Administration (2.5), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

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

| Lopinavir and Ritonavir Dosage Form | Recommended Dosage |
|---|---|
| 200 mg/50 mg Tablets | 800 mg/200 mg (4 tablets) once daily |
| 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 Tablets Twice Daily Regimen**

| Lopinavir and Ritonavir Dosage Form | Recommended Dosage |
|---|---|
| 200 mg/50 mg Tablets | 400 mg/100 mg (2 tablets) twice daily |
| 80 mg/20 mg per mL Oral Solution | 400 mg/100 mg (5 mL) twice daily |

The dose of lopinavir and ritonavir tablets 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 tablets is taken in combination with these agents.

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

| Lopinavir and Ritonavir Dosage Form | Recommended Dosage |
|---|---|
| 200 mg/50 mg Tablets and 100 mg/25 mg Tablets | 500 mg/125 mg (2 tablets of 200 mg/50 mg + 1 tablet of 100 mg/25 mg) twice daily |
| 80 mg/20 mg per mL Oral Solution | 520 mg/130 mg (6.5 mL) twice daily |

**2.4 Dosage Recommendations in Pediatric Patients**

Lopinavir and ritonavir tablets and oral solution are not recommended for once daily dosing in pediatric patients younger than 18 years of age. The dose of the oral solution should be administered using the calibrated cup (supplied) or oral dosing syringe. Lopinavir and ritonavir 100/25 mg tablets should be considered only in children who have reliably demonstrated the ability to swallow the intact tablet.

Lopinavir and ritonavir oral solution is not recommended in 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 ethanol and propylene glycol. Total amounts of ethanol 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 tablets 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:

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

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

*Based on Weight:*

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

*Based on BSA:*

Patient BSA ($m^2$) × Prescribed lopinavir dose ($mg/m^2$) = Administered lopinavir dose (mg)

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) ÷ 80 (mg/mL)

*Oral Solution Dosage Recommendation in Pediatric Patients 14 Days to Less Than 18 Years:*

Table 4 summarizes the recommended daily dosing regimen for pediatric patients 14 days to less than 18 years of age using the oral solution.

Lopinavir and ritonavir administered in combination with efavirenz, nevirapine, or nelfinavir in patients younger than 6 months of age is not recommended. Total dose of lopinavir and ritonavir oral solution in pediatric patients should not exceed the recommended adult daily dose of 400/100 mg (5mL) twice daily.

**Table 4. Lopinavir and Ritonavir Oral Solution Daily Dosage Recommendations in Pediatric Patients 14 days to Less Than 18 Years Without Concomitant Efavirenz, Nevirapine, or Nelfinavir**

| Patient Age | Based on Weight (mg/kg) | | Based on BSA ($mg/m^2$) | Frequency |
|---|---|---|---|---|
| 14 days to 6 months | 16/4 | | 300/75 | Given twice daily |
| Older than 6 months to less than 18 years | Less than15 kg | 12/3 | 230/57.5 | Given twice daily |
| | 15 kg to 40 kg | 10/2.5 | | |

*Tablet Dosage Recommendation in Pediatric Patients Older than 6 Months to Less than 18 Years:*

Table 5 provides the dosing recommendations for pediatric patients older than 6 months to less than 18 years of age based on body weight or body surface area for lopinavir and ritonavir tablets.

**Table 5. Lopinavir and Ritonavir Tablet Daily Dosage Recommendations in Pediatric Patients > 6 Months to < 18 Years of Age Without Concomitant Efavirenz, Nevirapine, or Nelfinavir**

| Body Weight (kg) | Body Surface Area ($m^2$)* | Recommended number of 100/25 mg Tablets Twice Daily |
|---|---|---|
| ≥15 to 25 | ≥0.6 to < 0.9 | 2 |
| >25 to 35 | ≥0.9 to < 1.4 | 3 |
| >35 | ≥1.4 | 4 |

* Lopinavir and ritonavir oral solution is available for children with a BSA less than 0.6 $m^2$ or those who are unable to reliably swallow a tablet.

Concomitant Therapy: Efavirenz, Nevirapine, or Nelfinavir

*Dosing recommendations using oral solution*

Table 6 provides the dosing recommendations for pediatric patients older than 6 months to less than 18 years of age based on body weight or body surface area for lopinavir and ritonavir oral solution when given in combination with efavirenz, nevirapine, or nelfinavir:

**Table 6. Lopinavir and Ritonavir Oral Solution Daily Dosage Recommendations for Pediatric Patients > 6 Months to < 18 Years of Age With Concomitant Efavirenz, Nevirapine, or Nelfinavir**

| Patient Age | Based on Weight (mg/kg) | | Based on BSA ($mg/m^2$) | Frequency |
|---|---|---|---|---|
| > 6 months to < 18 years | <15 kg | 13/3.25 | 300/75 | Given twice daily |
| | ≥15 kg to 45 kg | 11/2.75 | | |

*Dosing recommendations using tablets*

Table 7 provides the dosing recommendations for pediatric patients older than 6 months to less than 18 years of age based on body weight or body surface area for lopinavir and ritonavir tablets when given in combination with efavirenz, nevirapine, or nelfinavir.

**Table 7. Lopinavir and Ritonavir Tablet Daily Dosage Recommendations for Pediatric Patients > 6 Months to < 18 Years of Age With Concomitant Efavirenz†, Nevirapine, or Nelfinavir†**

| Body Weight (kg) | Body Surface Area ($m^2$)* | Recommended number of 100/25 mg Tablets Twice Daily |
|---|---|---|
| ≥15 to 20 | ≥0.6 to < 0.8 | 2 |
| >20 to 30 | ≥0.8 to < 1.2 | 3 |
| >30 to 45 | ≥1.2 to <1.7 | 4 |
| >45 | ≥1.7 | 5 *[see Dosage and Administration (2.4)]* |

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

**2.5 Dosage Recommendations in Pregnancy**

Administer 400/100 mg of lopinavir and ritonavir tablets twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions.

- Once daily lopinavir and ritonavir tablet 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 tablets are 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 Tablets USP,** containing 200 mg lopinavir and 50 mg ritonavir are light yellow film-coated ovaloid tablets debossed with 'X' on one side and '28' on other side.
- **Lopinavir and Ritonavir Tablets USP,** containing 100 mg lopinavir and 25 mg ritonavir are light yellow film-coated capsule shaped tablets debossed with 'D91' on one side and plain on other side.

**4 CONTRAINDICATIONS**

- Lopinavir and ritonavir tablets are 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 tablets are 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 *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.
  - Alpha 1- Adrenoreceptor Antagonist : alfuzosin
  - Antianginal: ranolazine
  - Antiarrhythmic: dronedarone
  - Anti-gout: colchicine
  - Antipsychotics: lurasidone, pimozide
  - Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine
  - GI Motility Agent: cisapride
  - Hepatitis C direct acting antiviral: elbasvir/grazoprevir
  - HMG-CoA Reductase Inhibitors: lovastatin, simvastatin
  - Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide
  - PDE5 Inhibitor: sildenafil (Revatio®) when used for the treatment of pulmonary arterial hypertension
  - Sedative/Hypnotics: triazolam, orally administered midazolam
- Lopinavir and ritonavir tablets are 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 *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.
  - Anticancer Agents: apalutamide
  - Antimycobacterial: rifampin
  - Herbal Products: St. John's Wort (hypericum perforatum)

**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 12 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 ethanol and propylene glycol. 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 ethanol 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 (2.4)* 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/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 to 6.3% of patients taking once daily lopinavir and ritonavir and 1.8 to 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 8):

**Table 8. 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 | % |
|---|---|---|
| **BLOOD AND LYMPHATIC SYSTEM DISORDERS** | | |
| anemia* | 54 | 2.1 |
| leukopenia and neutropenia* | 44 | 1.7 |
| lymphadenopathy* | 35 | 1.3 |
| **CARDIAC DISORDERS** | | |
| atherosclerosis such as myocardial infarction* | 10 | 0.4 |
| atrioventricular block* | 3 | 0.1 |
| tricuspid valve incompetence* | 3 | 0.1 |
| **EAR AND LABYRINTH DISORDERS** | | |
| vertigo* | 7 | 0.3 |
| tinnitus | 6 | 0.2 |
| **ENDOCRINE DISORDERS** | | |
| hypogonadism* | 16 | 0.8[1] |
| **EYE DISORDERS** | | |
| visual impairment* | 8 | 0.3 |
| **GASTROINTESTINAL DISORDERS** | | |
| 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 |
| **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** | | |
| fatigue including asthenia* | 198 | 7.6 |
| **HEPATOBILIARY DISORDERS** | | |
| hepatitis including AST, ALT, and GGT increases* | 91 | 3.5 |
| hepatomegaly | 5 | 0.2 |
| cholangitis | 3 | 0.1 |
| hepatic steatosis | 3 | 0.1 |
| **IMMUNE SYSTEM DISORDERS** | | |
| hypersensitivity including urticaria and angioedema* | 70 | 2.7 |
| immune reconstitution syndrome | 3 | 0.1 |
| **INFECTIONS AND INFESTATIONS** | | |
| upper respiratory tract infection* | 363 | 13.9 |
| lower respiratory tract infection* | 202 | 7.7 |
| skin infections including cellulitis, folliculitis, and furuncle* | 86 | 3.3 |
| **METABOLISM AND NUTRITION DISORDERS** | | |
| 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 |
| **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** | | |
| 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 |
| **NERVOUS SYSTEM DISORDERS** | | |
| 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 |
| **PSYCHIATRIC DISORDERS** | | |
| anxiety* | 101 | 3.9 |
| abnormal dreams* | 19 | 0.7 |
| libido decreased | 19 | 0.7 |
| **RENAL AND URINARY DISORDERS** | | |
| renal failure* | 31 | 1.2 |
| hematuria* | 20 | 0.8 |
| nephritis* | 3 | 0.1 |
| **REPRODUCTIVE SYSTEM AND BREAST DISORDERS** | | |
| erectile dysfunction* | 34 | 1.7[1] |
| menstrual disorders - amenorrhea, menorrhagia* | 10 | 1.7[2] |
| **SKIN AND SUBCUTANEOUS TISSUE DISORDERS** | | |
| 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 |
| **VASCULAR DISORDERS** | | |
| hypertension* | 47 | 1.8 |
| deep vein thrombosis* | 17 | 0.7 |

*Represents a medical concept including several similar MedDRA PTs
1. Percentage of male population (N=2,038)
2. Percentage of female population (N=574)

*Laboratory Abnormalities in Adults*

The percentages of adult patients treated with combination therapy with Grade 3 to 4 laboratory abnormalities are presented in Table 9 (treatment-naïve patients) and Table 10 (treatment-experienced patients).

**Table 9. Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients**

| | | Study 863 (48 Weeks) | | Study 720 (360 Weeks) | Study 730 (48 Weeks) | |
|---|---|---|---|---|---|---|
| **Variable** | **Limit[1]** | **Lopinavir and Ritonavir 400/100 mg Twice Daily + d4T +3TC (N = 326)** | **Nelfinavir 750 mg Three Times Daily + d4T + 3TC (N = 327)** | **Lopinavir and Ritonavir Twice Daily + d4T + 3TC (N = 100)** | **Lopinavir and Ritonavir Once Daily + TDF +FTC (N=333)** | **Lopinavir and Ritonavir Twice Daily + T

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 (2.5) 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 ethanol content. Lopinavir and ritonavir oral solution contains the excipients ethanol and propylene glycol.

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. The prevalence of birth defects in live births was 2.1% (95% CI: 1.4% to 3.0%) following first-trimester exposure to lopinavir-containing regimens and 3.0% (95% CI: 2.4% to 3.8%) following second and third trimester exposure to lopinavir-containing regimens. 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). The prevalence of birth defects in live births was 2.2% (95% CI: 1.7% to 2.8%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4% to 3.6%) following second and third trimester exposure to ritonavir- containing regimens. 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 administered lopinavir in combination with ritonavir (on gestation days 6 to 17) at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7 times (for lopinavir) and 1.8 times (for ritonavir) the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily). In a pre-and post-natal 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 administered lopinavir in combination with ritonavir (on gestation days 6 to 18) at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6 times (for lopinavir) and similar to (for ritonavir) 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: 1) HIV transmission (in HIV-negative infants), 2) developing viral resistance (in HIV- positive infants), and 3) adverse reactions in the breastfed infant, instruct mothers not to breastfeed if they are receiving lopinavir and ritonavir.

**8.3 Females and Males of Reproductive Potential**

Contraception

Use of lopinavir and ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)]*.

**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$^2$ twice daily plus two NRTIs in HIV-infected infants ≥14 days and < 6 months of age. Results revealed that infants younger than 6 months of age generally had lower lopinavir $AUC_{12}$ 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$^2$ oral solution twice daily regimen without nevirapine and the 300/75 mg/m$^2$ 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$^2$ twice daily + ≥ 2 NRTIs; Group 2: 480/120 mg/m$^2$ twice daily + ≥ 1 NRTI + 1 NNRTI) in 26 children and adolescents ≥ 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+ 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)]*.

A prospective multicenter, randomized, open-label study evaluated the efficacy and safety of twice-daily versus once-daily dosing of lopinavir and ritonavir tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included lopinavir and ritonavir, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, efficacy (defined as the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL) was significantly higher in subjects receiving twice daily dosing compared to subjects receiving once daily dosing. The safety profile was similar between the two treatment arms although there was a greater incidence of diarrhea in the once daily treated subjects.

**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.

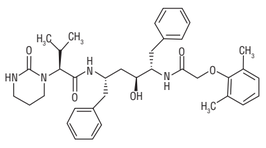
Lopinavir and ritonavir oral solution contains ethanol and propylene glycol. Ingestion of the product over the recommended dose by an infant or a young child could result in significant toxicity and could potentially be lethal.

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

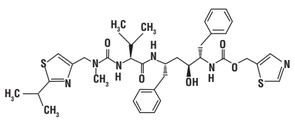
**11 DESCRIPTION**

Lopinavir and ritonavir tablets, USP are a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 protease. As co-formulated in lopinavir and ritonavir tablets USP, 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 powder. It is very soluble to freely soluble in methanol, freely soluble in alcohol, soluble in isopropanol, 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, crystalline powder. It is freely soluble in methanol and in methylene chloride, very slightly soluble in acetonitrile, practically insoluble in water. Ritonavir has the following structural formula:



Lopinavir and ritonavir tablets USP are available for oral administration in two strengths:

- Light yellow tablets containing 200 mg of lopinavir USP and 50 mg of ritonavir USP
- Light yellow tablets containing 100 mg of lopinavir USP and 25 mg of ritonavir USP.

The light yellow lopinavir and ritonavir tablets USP, 100 mg/25 mg and 200 mg/50 mg tablets contain the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide, poloxamer 188, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, polyethylene glycol 400, polysorbate 80, titanium dioxide, and ferric oxide yellow.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Lopinavir and ritonavir is a fixed-dose combination of HIV-1 antiviral drugs lopinavir *[see Microbiology (12.4)]* and ritonavir. As co-formulated in lopinavir and ritonavir, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

**12.2 Pharmacodynamics**

Cardiac Electrophysiology

The effect of lopinavir and ritonavir on QTcF interval was evaluated in a placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 39 healthy adults. 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. 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)]*.

**12.3 Pharmacokinetics**

The pharmacokinetic properties of lopinavir are summarized in Table 13. The steady-state pharmacokinetic parameters of lopinavir are summarized in Table 14. Under fed conditions, lopinavir concentrations were similar following administration of lopinavir and ritonavir tablets to capsules with less pharmacokinetic variability. Under fed conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of lopinavir and ritonavir capsules and oral solution.

**Table 13. Pharmacokinetic Properties of Lopinavir**

| **Absorption** | |
|---|---|
| $T_{max}$ (hr)[a] | 4.4 ± 0.8 |
| Effect of meal (relative to fasting)<br>Tablet<br>Oral solution | <br>↑ 19%[b]<br>↑ 130%[b] |
| **Distribution** | |
| % Bound to human plasma proteins | > 98 |
| $V_d/F$[a] (L) | 16.9 |
| **Metabolism** | |
| Metabolism | CYP3A |
| **Elimination** | |
| Major route of elimination | hepatic |
| $t_{1/2}$ (h)[a] | 6.9 ± 2.2 |
| % of dose excreted in urine | 10.4 ± 2.3 |
| % of dose excreted in feces | 82.6 ± 2.5 |

a. Lopinavir and ritonavir tablet
b. Changes in AUC values

**Table 14. Steady-State Pharmacokinetic Parameters of Lopinavir, Mean ± SD**

| Pharmacokinetic Parameter | Twice Daily[a] | Once Daily[b] |
|---|---|---|
| $C_{max}$ (µg/mL) | 9.8 ± 3.7 | 11.8 ± 3.7 |
| $C_{min}$ (µg/mL) | 5.5 ± 2.7 | 1.7 ± 1.6 |
| $AUC_{tau}$ (µg•h/mL) | 92.6 ± 36.7 | 154.1 ± 61.4 |

a. 19 HIV-1 subjects, lopinavir and ritonavir 400/100 mg twice daily
b. 24 HIV-1 subjects, lopinavir and ritonavir 800/200 mg + emtricitabine 200 mg + tenofovir DF 300 mg

Specific Populations

*Gender, Race and Age*

No gender or race related pharmacokinetic differences have been observed in adult patients. Lopinavir pharmacokinetics have not been studied in elderly patients.

*Pediatric Patients*

The 230/57.5 mg/m$^2$ twice daily regimen without nevirapine and the 300/75 mg/m$^2$ 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.

**Table 15. Lopinavir Pharmacokinetic Data from Pediatric Clinical Trials, Mean ± SD**

| $C_{max}$ (µg/mL) | $C_{min}$ (µg/mL) | $AUC_{12}$ (µg•hr/m) |
|---|---|---|
| **Age ≥ 14 Days to < 6 Weeks Cohort (N = 9):** | | |
| 5.17 ± 1.84[a] | 1.40 ± 0.48[a] | 43.39 ± 14.80[a] |
| **Age ≥ 6 Weeks to < 6 Months Cohort (N = 18):** | | |
| 9.39 ± 4.91[a] | 1.95 ± 1.80[a] | 74.50 ± 37.87[a] |
| **Age ≥ 6 Months to ≤ 12 years Cohort (N = 24):** | | |
| 8.2 ± 2.9[b] | 3.4 ± 2.1[b] | 72.6 ± 31.1[b] |
| 10.0 ± 3.3[c] | 3.6 ± 3.5[c] | 85.8 ± 36.9[c] |

a. Lopinavir and ritonavir oral solution300/75 mg/m$^2$ twice daily without concomitant NNRTI therapy
b. Lopinavir and ritonavir oral solution 230/57.5 mg/m$^2$ twice daily without nevirapine (n=12)
c. Lopinavir and ritonavir oral solution 300/75 mg/m$^2$ twice daily with nevirapine (n=12)

*Pregnancy*

The $C_{12h}$ values of lopinavir were lower during the second and third trimester by approximately 40% as compared to post-partum in 12 HIV-infected pregnant women received lopinavir and ritonavir 400 mg/100 mg twice daily. Yet 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 *[see Use in Specific Populations (8.1)]*.

*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*

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). 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*. 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.

The effects of co-administration of lopinavir and ritonavir on the AUC, $C_{max}$ and $C_{min}$ are summarized in Table 16 (effect of other drugs on lopinavir) and Table 17 (effect of lopinavir and ritonavir on other drugs). For information regarding clinical recommendations, see Table 12 in *Drug Interactions (7)*.

**Table 16. 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 | $C_{min}$ |
| Efavirenz[1] | 600 at bedtime | 400/100 capsule twice daily | 11, 7[3] | 0.97 (0.78, 1.22) | 0.81 (0.64, 1.03) | 0.61 (0.38, 0.97) |
| | 600 at bedtime | 500/125 tablet twice daily | 19 | 1.12 (1.02, 1.23) | 1.06 (0.96, 1.17) | 0.90 (0.78, 1.04) |
| | 600 at bedtime | 600/150 tablet twice daily | 23 | 1.36 (1.28, 1.44) | 1.36 (1.28, 1.44) | 1.32 (1.21, 1.44) |
| 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[2] | 700 twice daily plus ritonavir 100 twice daily | 400/100 capsule twice daily | 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 | 12 | 0.89 (0.80, 0.99) | 0.87 (0.75, 1.00) | 0.75 (0.55, 1.00) |
| Nelfinavir | 1000 twice daily | 400/100 capsule twice daily | 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 | 400/100 capsule twice daily | 22, 19[3] | 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; twice daily 1 wk[5] | (> 1 yr) 300/ 75 mg/m$^2$ oral solution twice daily | 12, 15[3] | 0.86 (0.64, 1.16) | 0.78 (0.56, 1.09) | 0.45 (0.25, 0.81) |
| Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir[2] | 25/150/100 + dasabuvir 400 | 400/100 tablet twice daily | 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) |
| 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) |
| 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) |
| Rifabutin | 150 once daily | 400/100 capsule twice daily | 14 | 1.08 (0.97, 1.19) | 1.17 (1.04, 1.31) | 1.20 (0.96, 1.65) |
| Rifampin | 600 once daily | 400/100 capsule twice daily | 22 | 0.45 (0.40, 0.51) | 0.25 (0.21, 0.29) | 0.01 (0.01, 0.02) |
| | 600 once daily | 800/200 capsule twice daily | 10 | 1.02 (0.85, 1.23) | 0.84 (0.64, 1.10) | 0.43 (0.19, 0.96) |
| | 600 once daily | 400/400 capsule twice daily | 9 | 0.93 (0.81, 1.07) | 0.98 (0.81, 1.17) | 1.03 (0.68, 1.56) |
| Rilpivirine | 150 once daily | 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 | 100 twice daily | 400/100 capsule twice daily | 8, 21[3] | 1.28 (0.94, 1.76) | 1.46 (1.04, 2.06) | 2.16 (1.29, 3.62) |
| Tipranavir/ ritonavir | 500/200 twice daily | 400/100 capsule twice daily | 21 69[3] | 0.53 (0.40, 0.69) | 0.45 (0.32, 0.63) | 0.30 (0.17, 0.51) |
| | | | | | | 0.48[4] (0.40, 0.58) |

1 Reference for comparison is lopinavir/ritonavir 400/100 mg twice daily without efavirenz.
2 Data extracted from the U.S. prescribing information of co-administered drugs.
3 Parallel group design
4 Drug levels obtained at 8 to 16 hours post dose
N/A = Not available.

**Table 17. 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 | | |
|---|---|---|---|---|---|---|
| | | | | $C_{max}$ | AUC | $C_{min}$ |
| Bedaquiline[1] | 400 single dose | 400/100 twice daily | N/A | N/A | 1.22 (1.11, 1.34) | N/A |
| Efavirenz | 600 at bedtime | 400/100 capsule twice daily | 11, 12[3] | 0.91 (0.72, 1.15) | 0.84 (0.62, 1.15) | 0.84 (0.58, 1.20) |
| Elbasvir/ grazoprevir[1] | 50 once daily | 400/100 twice daily | 10 | 2.87 (2.29, 3.58) | 3.71 (3.05, 4.53) | 4.58 (3.72, 5.64) |
| | 200 once daily | | 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 (Ortho Novum®) | 400/100 capsule twice daily | 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 tablet twice day | 16 | 0.70 (0.64-0.78) | 0.65 (0.59-0.71) | 0.55 (0.49-0.62) |
| Fosamprenavir[1] | 700 twice daily plus ritonavir 100 twice daily | 400/100 capsule twice daily | 18 | 0.42 (0.30, 0.58) | 0.37 (0.28, 0.49) | 0.35 (0.27, 0.46) |
| Indinavir | 600 twice daily combo nonfasting vs. 800 three times daily alone fasting | 400/100 capsule twice daily | 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 | 12 | 1.13 (0.91, 1.40) | 3.04 (2.44, 3.79) | N/A |
| Maraviroc[1] | 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 | 11 | 0.55 (0.48, 0.64) | 0.47 (0.42, 0.53) | N/A |
| Nelfinavir | 1000 twice daily combo vs. 1250 twice daily alone | 400/100 capsule twice daily | 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 twice daily | 400/100 capsule twice daily | 5, 6[3] | 1.05 (0.72, 1.52) | 1.08 (0.72, 1.64) | 1.15 (0.71, 1.86) |
| Norethindrone | 1 once daily (Ortho Novum®) | 400/100 capsule twice daily | 12 | 0.84 (0.75, 0.94) | 0.83 (0.73, 0.94) | 0.68 (0.54, 0.85) |
| Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir[1] | 25/150/100 + dasabuvir 400 | 400/100 tablet twice daily | 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[1] | 4 once daily | 400/100 tablet twice daily | 23 | 0.96 (0.84-1.10) | 0.80 (0.73-0.87) | N/A |
| Pravastatin | 20 once daily | 400/100 capsule twice daily | 12 | 1.26 (0.87, 1.83) | 1.33 (0.91, 1.94) | N/A |
| Rifabutin | 150 once daily combo vs. 300 once daily alone | 400/100 capsule twice daily | 12 | 2.12 (1.89, 2.38) | 3.03 (2.79, 3.30) | 4.90 (3.18, 5.76) |
| 25-*O*-desacetyl rifabutin | | | | 23.6 (13.7, 25.3) | 47.5 (29.3, 51.8) | 94.9 (74.0, 122) |
| Rifabutin + 25-*O*-desacetyl rifabutin | | | | 3.46 (3.07, 3.91) | 5.73 (5.08, 6.46) | 9.53 (7.56, 12.01) |
| Rilpivirine | 150 once daily | 400/100 capsules twice daily | 15 | 1.29 (1.18-1.40) | 1.52 (1.36-1.70) | 1.74 (1.46-2.08) |
| Rosuvastatin[2] | 20 once daily | 400/100 tablet twice daily | 15 | 4.66 (3.4, 6.4) | 2.08 (1.66, 2.6) | 1.04 (0.9, 1.2) |
| Tenofovir alafenamide[1] | 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[1] | 300 once daily | 400/100 capsule twice daily | 24 | No Change | 1.32 (1.26, 1.38) | 1.51 (1.32, 1.66) |

1 Data extracted from the U.S. prescribing information of co-administered drugs.
2 Kiser, et al. J Acquir Immune Defic Syndr. 2008 Apr 15; 47(5):570-8.
3 Parallel group design
N/A = Not available.

**12.4 Microbiology**

Mechanism of Action

Lopinavir, an inhibitor of the HIV-1 protease, prevents cleavage of the viral Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral Activity

In the absence of human serum, the mean 50% effective concentration ($EC_{50}$) values of lopinavir against five different HIV-1 subtype B laboratory strains in lymphoblastic cell lines ranged from 10 to 27 nM (0.006 to 0.017 µg/mL, 1 µg/mL = 1.6 µM), and ranged from 4 to 11 nM (0.003 to 0.007 µg/mL) against several HIV-1 subtype B clinical isolates in peripheral blood lymphocytes (n = 6). In the presence of 50% human serum, the mean $EC_{50}$ values of lopinavir against these five HIV-1 laboratory strains ranged from 65 to 289 nM (0.04 to 0.18 µg/mL), representing a 7 to 11-fold attenuation. The $EC_{50}$ values of lopinavir against three different HIV-2 strains ranged from 12 to 180 nM (0.008 to 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.

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 specific amino acid substitutions could be associated with resistance to lopinavir and ritonavir in the virus from 37 evaluable lopinavir and ritonavir-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. All four of these patients had previously received treatment with at least one protease inhibitor and 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.

Cross-resistance - Nonclinical Studies

Varying degrees of cross-resistance have been observed among HIV-1 protease inhibitors. The antiviral activity in cell culture of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined (Table 18).

**Table 18. Susceptibility Reduction to Lopinavir Against Isolates from Patients Previously Treated With a Single Protease Inhibitor**

| Susceptibility reduced by >4 fold | Susceptibility reduced to LPV |
|---|---|
| Indinavir (n=16) | 5.7 fold |
| Nelfinavir (n=13) | <4 fold |
| Ritonavir (n=3) | 8.32 fold |
| Saquinavir (n=4) | <4 fold |

Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following section.

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 19 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 19. 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[1]**

| Number of protease inhibitor substitutions at baseline[1] | Study 888 (Single protease inhibitor-experienced[2], NNRTI-naïve) n=130 | Study 765 (Single protease inhibitor-experienced[3], NNRTI-naïve) n=56 | Study 957 (Multiple protease inhibitor-experienced[4], NNRTI-naïve) n=50 |
|---|---|---|---|
| 0 to 2 | 76/103 (74%) | 34/45 (76%) | 19/20 (95%) |
| 3 to 5 | 13/26 (50%) | 8/11 (73%) | 18/26 (69%) |
| 6 or more | 0/1 (0%) | N/A | 1/4 (25%) |

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

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 $EC_{50}$ values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold the wild-type $EC_{50}$ 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 20.

**Table 20. HIV-1 RNA Response at Week 48 by Baseline Lopinavir Susceptibility[1]**

| Lopinavir susceptibility[2] at baseline | HIV-1 RNA <400 copies/mL (%) | HIV-1 RNA <50 copies/mL (%) |
|---|---|---|
| < 10 fold | 25/27 (93%) | 22/27 (