Lopinavir and Ritonavir Oral Pellets 40 mg/10 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lopinavir and Ritonavir Oral Pellets 40mg/10mg safely and effectively. See full prescribing information for Lopinavir and Ritonavir Oral Pellets.

Lopinavir and Ritonavir Oral Pellets for Oral Use

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

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

----------DOSAGE AND ADMINISTRATION----------

Oral Pellets: The capsules should be opened and the contents should be sprinkled over sweetened porridge, which is at room temperature. The entire mixture should be swallowed immediately. Do not chew or crush. (2)

Pediatric Patients (14 days and older):

- Twice daily dose is based on body weight. (2.2)
- Do not use once daily administration in pediatric patients.

Concomitant Therapy in Pediatric Patients:

- Dose adjustments of Lopinavir and Ritonavir may be needed when co-administering with efavirenz, nevirapine, or nelfinavir. (2.2, 7.3)

Lopinavir and Ritonavir Oral Pellets 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 (2.2, 5.2)

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

- Oral Pellets: 40 mg Lopinavir and 10 mg Ritonavir per capsule (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)

Coadministration with:

- drugs highly dependent on CYP3A for clearance and for which elevated plasma levels may result in serious and/or life-threatening events. (4)
- 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 Oral Pellets 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 Pellets 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 in this patient population has not been established (2.2, 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, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov / medwatch

----------DRUG INTERACTIONS----------

Coadministration 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 5/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Lopinavir and Ritonavir Oral Pellets 40mg /10mg is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in 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

2.2 Pediatric Patients

Lopinavir and Ritonavir Oral Pellets should not be administered once daily in pediatric patients < 18 years of age.

Lopinavir and Ritonavir Oral Pellets 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)]*.

Dosage

The following table lists the number of capsules containing Lopinavir and Ritonavir Oral Pellets 40 mg/10 mg to be administered twice-daily, using a simplified weight band-based approach.

Weight Band	**Number of capsules containing Lopinavir and Ritonavir Oral Pellets 40 mg/10 mg* needed to prepare each dose**
5 kg to less than 6 kg	2 capsules (80 mg)
6 kg to less than 10 kg	3 capsules (120 mg)

10 kg to less than 14 kg	4 capsules (160 mg)
14 kg to less than 20 kg	5 capsules (200 mg)
20 kg to less than 25 kg	6 capsules (240 mg)
25 kg to less than 30 kg	7 capsules (280 mg)
30 kg to less than 35 kg	8 capsules (320 mg)
Greater than or equal to 35	10 capsules (adult dose, 400mg)

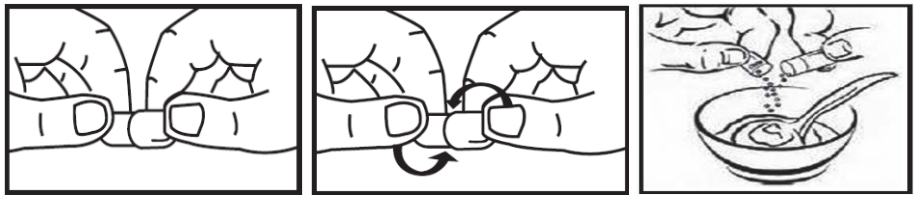
* without concomitant efavirenz, nevirapine, amprenavir or nelfinavir

Administration

Capsules containing Lopinavir and Ritonavir oral pellets should not be swallowed whole, and should be administered with food, as described below.

Method of administration:

- Place sweetened porridge, which is at room temperature, in a small bowl.
- Obtain the prescribed number of capsules needed for a dose.
- Hold both ends of the capsule between your fingertips as shown below.



- Twist the ends of the capsule in opposite direction and pull apart so that the entire content of the capsule is sprinkled over the sweetened porridge.
- Repeat this step for the prescribed number of capsules per dose. Ensure that the entire content of each capsule is sprinkled over the porridge.
- This drug/food mixture should be swallowed immediately. The oral pellets should not be chewed or crushed. It should not be stored for future use.
- Administration of the required dose should be followed by drinking water, to ensure that no pellets are left behind in the mouth.
- Repeat above steps for next dose.

Concomitant Therapy: Efavirenz, Nevirapine, or Nelfinavir

A dose increase of lopinavir/ritonavir to 300/75 mg/m^2 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 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.

However, precise dose titration may not be possible with Lopinavir and Ritonavir Oral Pellets. Thus, it is recommended that Lopinavir and ritonavir oral solution be used in this situation.

3 DOSAGE FORMS AND STRENGTHS

- **Lopinavir and Ritonavir Oral Pellets 40mg /10 mg**
  White to off white, circular biconvex, pelletsplain on both sides filled in size "1" hard gelatin capsules having clear transparent body with '414' spin printed in black ink and yellow cap with 'CL' spin printed in black ink.

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.
- Co-administration of lopinavir and ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions.
- Co-administration of Lopinavir and Ritonavir is contraindicated with potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance. These drugs are listed in Table 1.

Table 1. Drugs That Are Contraindicated With Lopinavir and Ritonavir

Drug Class	Drugs Within Class That are Contraindicated with Lopinavir and Ritonavir	Clinical Comments
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antimycobacterial	Rifampin	May lead to loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors or other co-administered antiretroviral agents *[see Drug Interactions (7)]*.
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.
Herbal Products	St John's Wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
PDE5 Enzyme Inhibitor	Sildenafil[a] (Revatio®) when used for the treatment of pulmonary arterial	A safe and effective dose has not been established when used with lopinavir and ritonavir. There is an increased potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope

	hypertension	*[see Drug Interactions (7)]*.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/Hypnotics	Triazolam; orally administered midazolam[b]	Prolonged or increased sedation or respiratory depression.
[a] see Drug Interactions (7), *Table 7* for coadministration of sidenafil in patients with erectile dysfunction. [b] see Drug Interactions (7), *Table 7* for parenterally administered midazolam.		

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Lopinavir and ritonavir is a CYP3A inhibitorInitiating treatment with lopinavir and ritonavir in patients receiving medications metabolized by CYP3A, or initiating 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 7 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 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 in this patient population has not been established. However, if the benefit of using lopinavir and ritonavir 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 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.

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 transminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as early as 7 days after the initiation of lopinavir/ritonavir in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however, a definitive casual relationship with lopinavir/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 maybe 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.

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)]*

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.

6.1 Adult Clinical Trial Experience

Treatment-Emergent Adverse Reactions

The safety of lopinavir and ritonavir has been investigated in about 2600 patients in Phase II-IV clinical trials, of which about 700 have received a dose of 800/200 mg 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 2):

Table 2. Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult Patients Receiving KALETRA 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
The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in Table 3 (treatment-naïve patients) and Table 4 (treatment-experienced patients).

Table 3. Grade 3-4 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 750mg Three Times Daily + d4T + 3TC (N = 327)**	**Lopinavir and Ritonavir Twice Daily +d4T + 3TC (N = 100)**	**Lopinavir and Ritonavir Once Daily + TDF + FTC (N = 333)**	**Lopinavir and Ritonavir Twice Daily + TDF + FTC (N = 331)**
Chemistry	**High**					
Glucose	>250mg/dL	2%	2%	4%	0%	<1%
Uric Acid	>12mg/dL	2%	2%	5%	<1%	1%
SGOT/ AST[2]	>180U/L	2%	4%	10%	1%	2%
SGPT/ ALT[2]	>215U/L	4%	4%	11%	1%	1%
GGT	>300U/L	N/A	N/A	10%	N/A	N/A
Total Cholesterol	>300mg/dL	9%	5%	27%	4%	3%
Triglycerides	>750mg/dL	9%	1%	29%	3%	6%
Amylase	>2 x ULN	3%	2%	4%	N/A	N/A
Lipase	>2 x ULN	N/A	N/A	N/A	3%	5%
Chemistry	**Low**					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	2%	2%
Hematolo	**Low**					

gy						
Neutrophils	<0.75x10^9/L	1%	3%	5%	2%	1%
[1] ULN = upper limit of the normal range; N/A = Not Applicable. [2] Criterion for Study 730 was >5xULN (AST/ALT).						

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

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

Hemoglobin	<80 g/L	1%	1%	1%	1%	2%

[1] ULN = upper limit of the normal range; N/A = Not Applicable.
[2] Includes clinical laboratory data from patients receiving 400/100 mg twice daily (n = 29) or 533/133 mg twice daily (n = 28) for 84 weeks. Patients received lopinavir and ritonavir in combination with NRTIs and efavirenz.
[3] Includes clinical laboratory data from patients receiving 400/100 mg twice daily (n = 36) or 400/200 mg twice daily (n = 34) for 144 weeks. Patients received lopinavir and ritonavir in combination with NRTIs and nevirapine.
[4] Criterion for Study 802 was >5x ULN (AST/ALT).

6.2 Pediatric Clinical Trial Experience

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

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

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

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

Laboratory Abnormalities

The percentages of pediatric patients treated with combination therapy including lopinavir and ritonavir with Grade 3-4 laboratory abnormalities are presented in Table 6.

Table 6. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients in Study 940

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

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

6.3 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/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 7.

Additionally, Lopinavir and Ritonavir induces glucuronidation.

7.2 Potential For Other Drugs To Affect Lopinavir

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

7.3 Established and Other Potentially Significant Drug Interactions

Table 7 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 7. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Lopinavir or Concomitant Drug**	**Clinical Comments**
HIV-1 Antiviral Agents		
HIV-1 Protease Inhibitor: fosamprenavir/ritonavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse reactions has been observed with co-administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: indinavir*	↑ indinavir	Decrease indinavir dose to 600 mg twice daily, when co-administered with lopinavir and ritonavir 400/100 mg twice daily *[see Clinical Pharmacology (12.3)]*. Lopinavir and ritonavir once daily has not been studied in combination with indinavir.
HIV-1 Protease Inhibitor: nelfinavir*	↑ nelfinavir ↑ M8 metabolite of nelfinavir ↓ lopinavir	Lopinavir and ritonavir should not be administered once daily in combination with nelfinavir *[see Clinical Pharmacology (12.3)]*.
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 Inihibitor: tipranavir	↓ lopinavir AUC and C_{min}	Lopinavir and ritonavir should not be administered with tipranavir (500 mg twice daily) co-administered with ritonavir (200 mg twice daily).
HIV CCR5–Antagonist: maraviroc	↑ maraviroc	Concurrent administration of maraviroc with Lopinavir and ritonavir will increase plasma levels of maraviroc. When co-administered, patients should receive 150 mg twice daily of maraviroc. For further details see complete prescribing information for Selzentry® (maraviroc).
Non-nucleoside Reverse Transcriptase Inibitors: efavirenz*, nevirapine*	↓ lopinavir	Lopinavir and Ritonavir dose increase is recommended in all patients *[see Clinical Pharmacology (12.3)]*. Lopinavir and ritonavir should not be administered once daily in combination with efavirenz or nevirapine *[see Clinical Pharmacology (12.3)]*.
Non-nucleoside Reverse Transcriptase Inibitor: delavirdine	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inibitor: didanosine		Lopinavir and ritonavir tablets can be administered simultaneously with didanosine without food. For Lopinavir and Ritonavir oral solution, 80 mg/mL and 20 mg/mL, 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, 80 mg/mL and 20 mg/mL (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir	↑ tenofovir	Lopinavir and ritonavir increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir and ritonavir and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside Reverse Transcriptase Inhibitor: abacavir zidovudine	↓ abacavir ↓ zidovudine	Lopinavir and ritonavir induces glucuronidation; therefore, lopinavir and ritonavir has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Other Agents		
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with lopinavir and ritonavir.
Anticancer Agents: vincristine, vinblastine, dasatinib, nilotinib	↑ anticancer agents	Concentrations of these drugs may be increased when co-administered with lopinavir/ritonavir resulting in the potential for increased adverse events usually associated with these anticancer agents. For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when lopinavir and ritonavir is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as lopinavir and ritonavir. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.
Anticoagulant: warfarin, rivaroxaban	↑ rivaroxaban	Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored. Avoid concomitant use of rivaroxaban and lopinavir and ritonavir. Coadministration of lopinavir and ritonavir and rivaroxaban is expected to result in increased exposure of rivaroxaban which may lead to risk of increased bleeding.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ lopinavir ↓ phenytoin	Lopinavir and ritonavir may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly and should be used

		with caution. Lopinavir and ritonavir should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin. In addition, co-administration of phenytoin and lopinavir and ritonavir may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with lopinavir and ritonavir.
Anticonvulsants: lamotrigine, valproate	↓ lamotrigine ↓ or ↔ valproate	Co-administration of lopinavir and ritonavir and lamotrigine or valproate may decrease the exposure of lamotrigine or valproate. A dose increase of lamotrigine or valproate may be needed when coadministered with lopinavir and ritonavir and therapeutic concentration monitoring for lamotrigine may be indicated; particularly during dosage adjustments *[see Clinical Pharmacology (12.3)]*.
Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Concurrent administration of bupropion with lopinavir and ritonavir may decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion). Patients receiving lopinavir and ritonavir and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and lopinavir and ritonavir may increase concentrations of trazodone. Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithomycin	↑ clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.

		• For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole, voriconazole	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole (>200 mg/day) or itraconazole (>200 mg/day) are not recommended. Co-administration of voriconazole with lopinavir and ritonavir has not been studied. However, a study has been shown that administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of lopinavir and ritonavir and voriconazole may result in decreased voriconazole concentrations and the potential for decreased voriconazole effectiveness and should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Otherwise, alternative antifungal therapies should be considered in these patients.
Anti-gout: colchicine	↑ colchicine	Patients with renal or hepatic impairment should not be given colchicine with lopinavir and ritonavir. <u>Treatment of gout flares-co-administration of colchicine in patients on Lopinavir and Ritonavir:</u> 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. <u>Prophylaxis of gout flares-co-administration of colchicine in patients on Lopinavir and Ritonavir:</u> If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original colchicine regimen was 0.6

		mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on Lopinavir and Ritonavir: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
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.
Antimycobacterial: rifampin	↓ lopinavir	May lead to loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors or other co-administered antiretroviral agents. A study evaluated combination of rifampin 600 mg once daily, with lopinavir and ritonavir 800/200 mg twice daily or lopinavir and ritonavir 400/100 mg + ritonavir 300 mg twice daily. Pharmacokinetic and safety results from this study do not allow for a dose recommendation. Nine subjects (28%) experienced a ≥ grade 2 increase in ALT/AST, of which seven (21%) prematurely discontinued study per protocol. Based on the study design, it is not possible to determine whether the frequency or magnitude of the ALT/AST elevations observed is higher than what would be seen with rifampin alone *[see Clinical Pharmacology (12.3) for magnitude of interaction]*.
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Antipsychotics: quetiapine	↑ quetiapine	Initiation of lopinavir and ritonavir in patients taking quetiapine: 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. Initiation of quetiapine in patients taking lopinavir and ritonavir: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Benzodiazepines: parenterally administered midazolam	↑ midazolam	Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, lopinavir and ritonavir should not be given with orally administered midazolam *[see Contraindications (4)]*. If lopinavir and ritonavir is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
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): budesonide, dexamethasone, prednisone	↓ lopinavir ↑ glucocorticoids	Use with caution. Lopinavir and ritonavir may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly. Concomitant use may result in increased steroid concentrations and reduced serum cortisol concentrations. Concomitant use of glucocorticoids that are metabolized by CYP3A, particularly for long-term use, should consider the potential benefit of treatment versus the risk of systemic corticosteroid effects. Concomitant use may increase the risk for development of

		systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.
Dihydropyridine Calcium Channel Blockers: e.g. felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Endothelin Receptor Antagonists: bosentan	↑ bosentan	<u>Co-administration of bosentan in patients on Lopinavir/Ritonavir:</u> In patients who have been receiving Lopinavir/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/Ritonavir in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of lopinavir/ritonavir. After at least 10 days following the initiation of Lopinavir/Ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
HCV-Protease Inhibitor: boceprevir	↓ lopinavir ↓ boceprevir ↓ ritonavir	It is not recommended to co-administer lopinavir and ritonavir and boceprevir. Concomitant administration of lopinavir and ritonavir and boceprevir reduced boceprevir, lopinavir and ritonavir steady-state exposures *[see Clinical Pharmacology (12.3)]*.
HCV-Protease Inhibitor: telaprevir	↓ telaprevir ↔ lopinavir	It is not recommended to co-administer lopinavir and ritonavir and telaprevir. Concomitant administration of lopinavir and ritonavir and telaprevir reduced steady-state telaprevir exposure, while the steady-state lopinavir exposure was not affected *[see Clinical Pharmacology (12.3)]*.
HMG-CoA Reductase Inibitors:	↑ atorvastatin ↑ rosuvastatin	Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin

atorvastatin rosuvastatin		dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. See Drugs with No Observed or Predicted Interactions with Lopinavir and Ritonavir *(7.4)* and Clinical Pharmacology *(12.3)* for drug interaction data with other HMG-CoA reductase inhibitors.
Imnunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir.
Inhaled or Intranasal Steroids e.g.: fluticasone, budesonide	↑ glucocorticoids	Concomitant use of lopinavir and ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use may result in increased steroid concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients when certain ritonavircontaining products have been co-administered with fluticasone propionate or budesonide.
Long-acting beta-adrenoceptor Agonist: salmeterol	↑ salmeterol	Concurrent administration of salmeterol and Lopinavir and Ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Narcotic Analgesic: methadone,* fentanyl	↓ methadone ↑ fentanyl	Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. Concentrations of fentanyl are expected to increase. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with lopinavir and ritonavir.
PDE5 inhibitors: avanafil, sildenafil,	↑ avanafil ↑ sildenafil ↑ tadalafil	Do not use lopinavir and ritonavir with avanafil because a safe and effective avanafil dosage regimen has not been

tadalafil, vardenafil	↑ vardenafil	established. Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving Lopinavir/Ritonavir. Co-administration of Lopinavir/Ritonavir with these drugs is expected to substantially increase their concentrations and may result in an increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection. Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): Sildenafil (Revatio®) is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) because a safe and effective dose has not been established when used with Lopinavir/Ritonavir *[see Contraindications (4)]*. The following dose adjustments are recommended for use of tadalafil (Adcirca®) with Lopinavir/Ritonavir: <u>Co-administration of ADCIRCA in patients on Lopinavir/Ritonavir:</u> In patients receiving Lopinavir/Ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. <u>Co-administration of Lopinavir/Ritonavir in patients on ADCIRCA:</u> Avoid use of ADCIRCA during the initiation of Lopinavir/Ritonavir. Stop ADCIRCA at least 24 hours prior to starting Lopinavir/Ritonavir. After at least one week following the initiation of Lopinavir/Ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

		Use of PDE5 inhibitors for erectile dysfunction: It is recommended not to exceed the following doses: • Sildenafil: 25 mg every 48 hours • Tadalafil: 10 mg every 72 hours • Vardenafil: 2.5 mg every 72 hours Use with increased monitoring for adverse events.
* *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), pitavastatin, pravastatin, stavudine, lamivudine, omeprazole, raltegravir, or ranitidine.

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C.

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

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

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily).

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving Lopinavir/Ritonavir.

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 once daily has not been evaluated 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 with 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 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)]*.

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

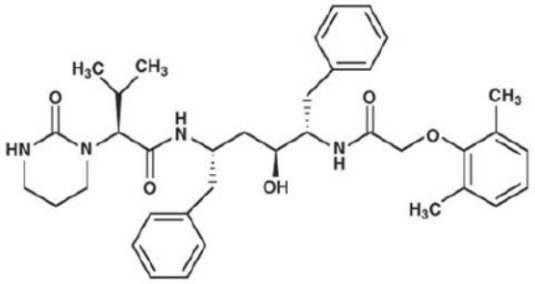
Overdoses with Lopinavir and Ritonavir oral solution, 80 mg/mL and 20 mg/mL have been reported. One of these reports described fatal cardiogenic shock in a 2.1 kg infant who received a single dose of 6.5 mL of Lopinavir and Ritonavir Oral Solution (520 mg lopinavir, approximately 10-fold above the recommended 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, 80 mg/mL and 20 mg/mL 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.

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 alcohol and propylene glycol in the case of overdose with lopinavir and ritonavir oral solution.

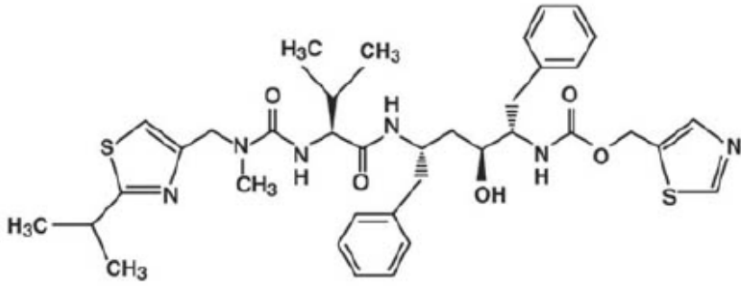
11 DESCRIPTION

Lopinavir and Ritonavir 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 Pellets are available for oral administration as 40 mg lopinavir and 10 mg ritonavir per capsule for sprinkling on food. Lopinavir and Ritonavir Oral Pellets also contain the following inactive ingredients: colloidal silicon dioxide, copovidone, hydroxy propyl methyl cellulose, polyethylene glycol 6000,sodium stearyl fumarate ,sorbitan monolaurate, and talc.The capsule shell contains the following inactive ingredients and dyes: gelatin, iron oxide yellow, sodium lauryl sulfate and titanium dioxide. The capsules are printed with ink containing black iron oxide, potassium hydroxide, and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

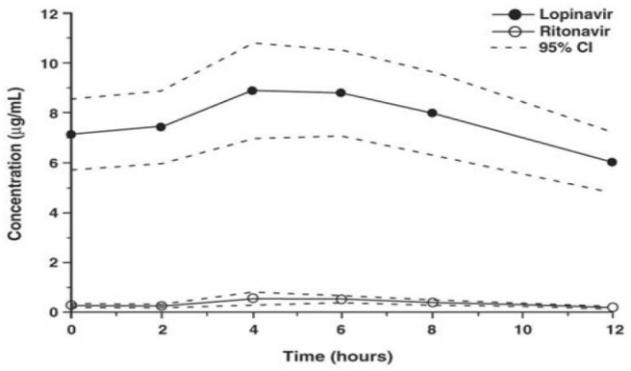
12.3 Pharmacokinetics

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_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Lopinavir and Ritonavir is due to lopinavir.

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

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



Absorption
In a pharmacokinetic study in HIV-1 positive subjects (n = 19), multiple dosing with 400/100 mg Lopinavir and Ritonavir twice daily with food for 3 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 µg/mL and minimum concentration within a dosing interval was 5.5 ± 2.7 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 µg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. 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.

Effects of Food on Oral Absorption
Lopinavir and Ritonavir Oral Solution, 80 mg/mL and 20 mg/mL
Relative to fasting, administration of Lopinavir and Ritonavir Oral Solution with a moderate fat meal (500 to 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, 80 mg/mL and 20 mg/mL should be taken with food.

Distribution

At steady state, lopinavir is approximately 98 to 99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg lopinavir and ritonavir twice daily, and is similar between healthy volunteers and HIV-1 positive patients.

Metabolism

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

Elimination

Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5.98 ± 5.75 L/hr (mean ± SD, n = 19).

Once Daily Dosing

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

The pharmacokinetics of once daily lopinavir and ritonavir has been evaluated in treatment experienced HIV-1 infected subjects. Lopinavir exposure (C_{max}, $AUC_{[0-24h]}$, C_{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^2 twice daily and 230/57.5 mg/m^2 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^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).

The mean steady-state lopinavir AUC, C_{max}, and C_{min} 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^2 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^2 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^2 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_{12}, C_{max}, and C_{12} 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^2 twice daily without concomitant NNRTI therapy.

The pharmacokinetics of Lopinavir and Ritonavir soft gelatin capsule and oral solution (Group 1: 400/100 mg/m^2 twice daily + 2 NRTIs; Group 2: 480/120 mg/m^2 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^2 resulted in high lopinavir exposure, as almost all subjects had lopinavir AUC_{12}

above 100 µg•h/mL. Both groups of subjects also achieved relatively high average minimum lopinavir concentrations.

Lopinavir and Ritonavir once daily has not been evaluated in pediatric patients.

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

Hepatic Impairment
Lopinavir is principally metabolized and eliminated by the liver. Multiple dosing of Lopinavir and Ritonavir 400/100 mg twice daily to HIV-1 and HCV co-infected patients with mild to moderate hepatic impairment (n = 12) resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV-1 infected subjects with normal hepatic function (n = 12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31%, respectively). Caution should be exercised when administering lopinavir and ritonavir to subjects with hepatic impairment. Lopinavir and ritonavir has not been studied in patients with severe hepatic impairment *[see Warnings and Precautions (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 8 (effect of other drugs on lopinavir) and Table 9 (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 7 in *Drug Interactions (7).*

Table 8. 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[12] (0.60, 0.72)	0.57 (0.49, 0.65)
Efavirenz [1,2]	600 at bed time, 9 d	400/100 capsule twice daily, 9d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 at bed time, 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 bed time, 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)
Fosamprenavir[3]	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)[4#]	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[5]	(> 1 yr) 300/75 mg/m^2 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)
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[6]	4 mg once daily, 5 d	400/100 tablet twice daily, 16 d	23	0.93 (0.88-0.98)	0.91 (0.86-0.97)	NA
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[7]	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[8]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
Ritonavir[4]	100 twice daily, 3-4 wk[#]	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)
Telaprevir	750 q8h, 10	400/100	12[13]	0.96 (0.87,	1.06 (0.96,	1.14 (0.96,

	days	tablet twice daily, 20 days		1.05)	1.17)	1.36)
Tenofovir[9]	300 mg once daily, 14 d	400/100 capsule twice daily, 14 d	24	NC†	NC†	NC†
Tipranavir/ ritonavir[4]	500/200 mg twice daily (28 doses)#	400/100 capsule twice daily (27doses)	21 69	0.53 (0.40, 0.69)[10]	0.45 (0.32, 0.63)[10]	0.30 (0.17, 0.51)[10] 0.48 (0.40,0.58)[11]

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/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 $AUC_{(0\text{-last})}$

[13] N=12 for test arm, 19 for reference arm

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

† 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 9. 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**	**n**	**Ratio (in combination with Lopinavir and Ritonavir/alone) of Co-administered Drug**

		Ritonavir (mg)		**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[8]	0.50 (0.45, 0.55)	0.55 (0.49, 0.61)	0.43 (0.36, 0.53)
Desipramine[2]	100 single dose	400/100 capsule twice daily, 10 d	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	N/A
Efavirenz	600 at bed time, 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)
Ethinyl Estradiol	35 µg once daily, 21 d (Ortho Novum®)	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)
Fosamprenavir[3]	700 twice daily plus ritonavir 100 twice daily, 14 d	400/100 capsule twice daily, 14d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir[1]	600 twice daily, 10 d combo nonfasting vs. 800 three times daily, 5d 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
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[1]	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®)	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)
Pitavastatin[4]	4 mg 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-*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[5]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Rosuvastatin[6]	20 mg 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)
Telaprevir	750 q8h, 10 days	400/100 tablet twice daily, 20 days	12[9]	0.47 (0.41, 0.52)	0.46 (0.41, 0.52)	0.48 (0.40, 0.56)
Tenofovir[7]	300 mg once daily, 14 d	400/100 capsule twice daily, 14 d	24	NC[†]	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] Ratio of parameters for indinavir, and nelfinavir, are not normalized for dose.
[2] Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.
[3] Data extracted from the fosamprenavir package insert.
[4] 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*).
[5] Effect on the dose-normalized sum of rifabutin parent and 25-*O*-desacetyl rifabutin active metabolite.
[6] Kiser, et al. J Acquir Immune Defic Syndr. 2008 Apr 15;47(5):570-8.
[7] Data extracted from the tenofovir package insert.
[8] N=12 for C_{min} (test arm)
[9] N=12 for the test arm, 14 for reference arm
* 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_{50}) values of lopinavir against five different HIV-1 subtype B laboratory strains 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 (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 to18 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_{50} values of lopinavir against three different HIV-2 strains ranged from 12 to180 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.

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-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 10 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 10. Virologic Response (HIV-l RNA<400copies/mL) at Week 48 by Baseline Lopinavir and Ritonavir Susceptibilty 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-naive) n=130	Study 765 (Single protease inhibitor-experienced[3], NNRTI-naive) n=56	Study 957 (Multiple protease inhibitor-experienced[4], NNRTI-naive) 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%)

[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 11.

Table 11. 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 (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/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 to 2.2 times (mice) and 0.5 times (rats) the human exposure (based on $AUC_{0\text{-}24hr}$ measurement) at the recommended dose of 400/100 mg Lopinavir and Ritonavir twice daily. Administration of lopinavir/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^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 2.6 to 6.8 $\log_{10}$ copies/mL).

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

Table 12. Outcomes of Randomized Treatment Through Week 48 (Study 863)

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

[1] Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.
[2] Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.
[3] Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through week 48, including patients who discontinued subsequent to virologic failure, was 17% in the Lopinavir/Ritonavir arm and 24% in the nelfinavir arm.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the Lopinavir 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 13.

Table 13. 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[1]	<50 copies/mL[2]	n	<400 copies/mL[1]	<50 copies/mL[2]	n
< 30,000	74%	71%	82	79%	72%	87
≥ 30,000 to < 100,000	81%	73%	79	67%	54%	79
≥ 100,000 to < 250,000	75%	64%	83	60%	47%	72
≥ 250,000	72%	60%	82	44%	33%	89

[1] Patients achieved and maintained confirmed HIV-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^3 for the Lopinavir and Ritonavir arm and 195 cells/mm^3 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^3 (range: 20 to 775 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.0 log_{10} copies/mL (range: 1.7 to 7.0 log_{10} copies/mL).

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

Table 14.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[1]	78%	77%
Virologic failure[2]	10%	8%
Rebound	5%	5%
Never suppressed through Week 48	5%	3%
Death	1%	<1%
Discontinued due to adverse event	4%	3%
Discontinued for other reasons[3]	8%	11%

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

Through 48 weeks of therapy, 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^3 for the Lopinavir and Ritonavir once daily arm and 198 cells/mm^3 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 (400/100mg 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^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 $\log_{10}$ copies/mL (range: 2.6 to 6.0 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 15.

Table 15. Outcomes of Randomized Treatment Through Week 48 (Study 888)

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

[1] Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.
[2] Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
[3] Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

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^3 for the Lopinavir and Ritonavir arm and 112 cells/ mm^3 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 to 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^3 (range: 4 to 952 cells/

mm^3) and mean baseline plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/mL (range: 1.7 to 6.6 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 16.

Table 16. 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[1]	22%	24%
No virologic data in Week 48 window		
Discontinued study due to adverse event or death[2]	5%	7%
Discontinued study for other reasons[3]	13%	12%
Missing data during window but on study	3%	3%

[1] 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.
[2] 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.
[3] 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^3 for the once daily group and 122 cells/ mm^3 for the twice daily groups.

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 to 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 to 918) and 372 (72 to 807) cells/mm^3, 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) $\log_{10}$ 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^3. 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^3. 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^2 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 to 6.0) weeks and all completed 24 weeks. At entry, median (range) HIV-1 RNA was 6.0 (4.7 to 7.2) $\log_{10}$ 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 to 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 to 25.7) weeks and 19 of 21 infants completed 24 weeks. At entry, median (range) HIV RNA level was 5.8 (3.7 to 6.9) $\log_{10}$ 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 to 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^2 or 300 mg lopinavir/75 mg ritonavir per m^2. 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^2 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^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ 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^3 for

antiretroviral naïve and 284 cells/mm^3 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^2 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^2 oral solution twice daily regimen without nevirapine and the 300/75mg/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). 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 400/100mg/m^2 or 480/120mg/m^2 (with efavirenz) twice daily, plasma concentrations were 60 to 100 % higher than among 6 to 12 year old patients receiving 230/57.5 mg/m^2. 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 actual patient dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lopinavir and Ritonavir Oral Pellets is available in the following strength and package size:

16.1 Lopinavir and Ritonavir Oral Pellets 40mg / 10mg

White to off white, circular biconvex, Oral Pellets plain on both sides filled in size "1" hard gelatin capsules having clear transparent body with '414' spin printed in black ink and yellow cap with 'CL' spin printed in black ink.

Bottles of 120 capsules. Each capsule contains 40 mg of lopinavir and 10 mg of ritonavir.

Recommended Storage

Store at room temperature below 30 ºC (86 ºF). For patient use: exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Information For Patients

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 pellets should be sprinkled over sweetened soft food, such as sweetened porridge. The food should be at room temperature, and the mixture is to be consumed immediately i.e. do not store the mixture for later use.
- 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, etc.**

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® (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® (salmeterol).
- If they are taking or before they begin taking Advair® (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® (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/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/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/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/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/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/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.

Lopinavir and Ritonavir Oral Pellets 40mg /10mg for Oral Use.

CIPLA LTD.
Verna Indl. Estate,
Goa 403 722 India.

Rev. 5/2015

MEDICATION GUIDE

Lopinavir and Ritonavir Oral Pellets, 40 mg / 10 mg

Read this Medication Guide before your child starts 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 the doctor about your child's medical condition or treatment. You and your child's doctor should talk about your child's treatment with lopinavir and ritonavir before your child starts taking it and at regular check-ups. Your child should stay under a doctor's care when taking lopinavir and ritonavir.

What is the most important information I should know about Lopinavir and Ritonavir Oral Pellets?

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 Oral Pellets?"
- **Changes in the heart rhythm and electrical activity of the heart.** These changes may be seen on an EKG (electrocardiogram) and can lead to serious heart problems. The risk for these problems may be higher if your child:
  - already has a history of abnormal heart rhythm or other types of heart disease.
  - takes other medicine(s) that can affect the heart rhythm while taking Lopinavir and Ritonavir.

Tell your child's doctor right away if your child has 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 Oral Pellets?

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 children 14 days of age and older. HIV-1 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 oral pellets contains two medicines: lopinavir and ritonavir.

When used with other HIV medicines, Lopinavir and Ritonavir may help to reduce the amount of HIV in the blood (called "viral load"). Lopinavir and Ritonavir may also help to increase the number of white blood cells called CD4 (T) cells which help fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your child's immune

system. This may reduce the risk of death or infections that can happen when your child's 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, etc.**

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

Who should not take Lopinavir and Ritonavir Oral Pellets?
Do not give Lopinavir and Ritonavir if your child takes any of the following medicines:

- alfuzosin (Uroxatral®)
- cisapride (Propulsid®, Quicksolv®)
- ergot containing medicines, including:
  - ergotamine tartrate (Cafergot®, Migergot®, Ergomar®, Ergostat®, Medihaler®, Ergotamine, Wigraine®, Wigrettes®)
  - dihydroergotamine mesylate (D.H.E. 45®, Migranal®)
  - methylergonovine (Methergine®)
- lovastatin (Advicor®, Altoprev®, Mevacor®)
- midazolam oral syrup
- pimozide (Orap®)
- rifampin (Rifadin®, Rifamate®, Rifater®, Rimactane®)
- sildenafil (Revatio®), when used for the treatment of pulmonary arterial hypertension
- simvastatin (Zocor®, Vytorin®, Simcor®)
- St. John's Wort (Hypericum perforatum)
- triazolam (Halcion®)

Serious problems or death can happen if your child takes any of the medicines listed above with Lopinavir and Ritonavir.

- **Do not give Lopinavir and Ritonavir Oral Pellets if your child is allergic** to lopinavir, ritonavir or any of the ingredients in Lopinavir and Ritonavir Oral Pellets. See the end of this Medication Guide for a complete list of ingredients in Lopinavir and Ritonavir Oral Pellets.

What should I tell the doctor before my child takes Lopinavir and Ritonavir Oral Pellets?
Lopinavir and Ritonavir may not be right for your child. Tell the doctor about all your child's medical conditions, including if your child:

- has any heart problems, including a condition called Congenital Long QT Syndrome.

- has or had pancreas problems.
- has liver problems, including Hepatitis B or Hepatitis C.
- has diabetes.
- has hemophilia. People who take Lopinavir and Ritonavir may have increased bleeding.
- has low potassium in the blood.

Tell the doctor about all the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements. Many medicines interact with Lopinavir and Ritonavir. Do not give your child a new medicine without telling the doctor or pharmacist. Your child's doctor can tell you if it is safe to give Lopinavir and Ritonavir with other medicines to your child. Your child's doctor may need to change the dose of other medicines while your child takes Lopinavir and Ritonavir Oral Pellets.

Especially tell the doctor if your child takes:
- medicines to treat HIV
- medicines to prevent organ transplant rejection
- medicines to treat cancer
- amiodarone (Cordarone®, Pacerone®)
- atorvastatin (Lipitor®)
- atovaquone (Marlarone®, Mepron®)
- bepridil (Bepadin®, Vascor®)
- boceprevir (Victrelis®)
- bosentan (Tracleer®)
- budesonide (Rhinocort®, Symbicort®, Pulmicort®, Entocort EC®)
- bupropion (Aplenzin®, Forfivo XL®, Wellbutrin®, Zyban®)
- carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)
- clarithromycin (Biaxin®, Prevpac®)
- colchicine (Colcrys®)
- dexamethasone (Maxidex®, Ozurdex®)
- disulfiram
- felodipine
- fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Subsys®)
- fluticasone (Cutivate®, Flonase®, Flovent®, Flovent Diskus®, Flovent HFA®, Veramyst®)
- itraconazole (Onmel®, Sporanox®)
- ketoconazole (Extina®, Ketozole®, Nizoral®, Xolegel®)
- lamotrigine (Lamictal®)
- lidocaine
- methadone hydrochloride (Dolphine hydrochloride, Methadose®)
- metronidazole
- nicardipine (Cardene®)
- nifedipine (Adalat CC®, Afeditab CR®, Procardia®)
- phenobarbital
- phenytoin (Dilantin®, Phenytek®)
- prednisone

- quetiapine (Seroquel®)
- quinidine (Quinidex®)
- rifabutin (Mycobutin®)
- rivaroxaban (Xarelto®)
- rosuvastatin (Crestor®)
- salmeterol (Serevent®) or salmeterol when taken in combination with fluticasone (Advair Diskus®, Advair HFA®)
- tadalafil (Adcirca®) for the treatment of pulmonary arterial hypertension
- telaprevir (Incivek®)
- trazodone (Oleptro®)
- valproate (Depakote®, Depakene®, Depacon®)
- voriconazole (Vfend®)
- warfarin (Coumadin®, Jantoven®)

Lopinavir and Ritonavir should not be administered once daily in combination with carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®), phenobarbital, or phenytoin (Dilantin®, Phenytek®)

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

Know all the medicines that your child takes. Keep a list of them with you to show doctors and pharmacists when your child gets a new medicine.

If you are not sure if your child is taking a medicine above, ask the doctor.

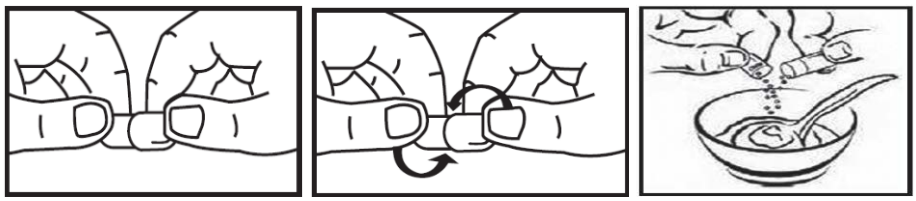
How should I take Lopinavir and Ritonavir Oral Pellets?
- Your child should take Lopinavir and Ritonavir Oral Pellets every day exactly as prescribed by the doctor.
- It is very important to set up a dosing schedule and follow it every day.
- Do not change your child's treatment or stop treatment without first talking with your child's doctor.
- Do not miss a dose of Lopinavir and Ritonavir Oral Pellets. This could make the virus harder to treat. If your child forgets to take Lopinavir and Ritonavir Oral Pellets, give the missed dose right away. If it is almost time for the next dose, do not give the missed dose. Instead, follow the regular dosing schedule by giving your child the next dose at its regular time. Do not give more than one dose of Lopinavir and Ritonavir to your child at one time.
- If your child takes more than the prescribed dose of Lopinavir and Ritonavir Oral Pellets, call your child's doctor or go to the nearest emergency room right away.
- If your child is prescribed Lopinavir and Ritonavir Oral Pellets, tell the doctor if your child's weight changes.

Weight Band (Kg)	**Number of Lopinavir and Ritonavir Oral Pellets***
5 kg to less than 6 kg	2 twice daily
6kg to less than 10 kg	3 twice daily
10 kg to less than 14 kg	4 twice daily
14 kg to less than 20 kg	5 twice daily
20 kg to less than 25 kg	6 twice daily
25 kg to less than 30 kg	7 twice daily
30 kg to less than 35 kg	8 twice daily
Greater than or equal to 35 kg	10 twice daily

* without concomitant efavirenz, nevirapine, amprenavir or nelfinavir

Method of administration:

- Place sweetened porridge, which is at room temperature, in a small bowl.
- Obtain the prescribed number of capsules needed for a dose.
- Hold both ends of the capsule between your fingertips as shown below.



- Twist the ends of the capsule in opposite direction and pull apart so that the entire content of the capsule is sprinkled over the sweetened porridge.
- Repeat this step for the prescribed number of capsules per dose. Ensure that the entire content of each capsule is sprinkled over the porridge.
- This drug/food mixture should be swallowed immediately. The oral pellets should not be chewed or crushed. It should not be stored for future use.
- Administration of the required dose should be followed by drinking water, to ensure that no pellets are left behind in the mouth.
- Repeat above steps for next dose.

- Lopinavir and Ritonavir **should not** be given one time each day in children.
- When the Lopinavir and Ritonavir Oral Pellets supply starts to run low, get more from your child's doctor or pharmacy. It is important not to run out of Lopinavir and Ritonavir. The amount of HIV-1 virus in your child's 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 Oral Pellets?"**

- **Inflammation of the pancreas (pancreatitis).** Some people who take Lopinavir and Ritonavir get inflammation of the pancreas which may be serious and cause death. Your child has a higher chance of getting pancreatitis if your child has had it before. Tell the doctor if your child has nausea, vomiting, or abdominal pain while taking Lopinavir and Ritonavir Oral Pellets. These may be signs of pancreatitis.
- **Liver problems.** Liver problems, including death, can happen in people who take Lopinavir and Ritonavir. Your child's doctor should do blood tests before and during your child's treatment with Lopinavir and Ritonavir Oral Pellets to check the 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 the doctor right away if your child has 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 the doctor if you often notice an increase in thirst or urination in your child while taking Lopinavir and Ritonavir.
- **Changes in your child's immune system (Immune Reconstitution Syndrome)** can happen when your child starts taking HIV medicines. Your child's immune system may get stronger and begin to fight infections that have been hidden in your child's body for a long time. Call the doctor right away if your child starts having new symptoms after starting HIV medicine.
- **Increases in certain fat (triglycerides and cholesterol) levels in your child's blood.** Large increases of triglycerides and cholesterol can be seen in blood test results of some people who take Lopinavir and Ritonavir. Your child's doctor should do blood tests to check your child's cholesterol and triglycerides levels before your child takes Lopinavir and Ritonavir and during the treatment.
- **Changes in body fat.** Changes in body fat have occurred in some people who take antiretroviral therapy. These changes may include an 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 the healthcare provider if your child had a rash when your child took another medicine for HIV-1 infection or if you notice any skin rash when your child takes lopinavir and ritonavir.

Common side effects of Lopinavir and Ritonavir include:
- diarrhea
- nausea
- increased fats in blood (triglycerides or cholesterol)

- vomiting

Tell your child's doctor about any side effect that bothers your child or that does not go away.

These are not all of the possible side effects of Lopinavir and Ritonavir. For more information, ask your child's doctor or pharmacist.

Call your child's 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 Oral Pellets?
Lopinavir and Ritonavir Oral Pellets:
- Store below 30°C (86°F)
- Do not keep Lopinavir and Ritonavir Oral Pellets out of the container for longer than 2 weeks, especially in areas where there is a lot of humidity. Keep the container tightly closed.

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

Keep Lopinavir and Ritonavir Oral Pellets 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 Oral Pellets for a condition for which it was not prescribed. Do not give Lopinavir and Ritonavir Oral Pellets to other people, even if they have the same condition your child has. 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 child's doctor. You can ask your child's pharmacist or doctor for information about Lopinavir and Ritonavir that is written for health professionals. For more information about Lopinavir and Ritonavir call 1-866-604-3268.

What are the ingredients in Lopinavir and Ritonavir Oral Pellets?
Active ingredient: lopinavir and ritonavir
Inactive ingredients:
Lopinavir and Ritonavir Oral Pellets 40mg/10mg: colloidal silicon dioxide, copovidone, hydroxy propyl methyl cellulose, polyethylene glycol 6000,sodium stearyl fumarate ,sorbitan monolaurate, and talc. The capsule shell contains the following inactive ingredients and dyes: gelatin, iron oxide yellow, sodium lauryl sulfate and titanium dioxide. The capsules are printed with ink containing black iron oxide, potassium hydroxide, and shellac.

This Medication Guide has been approved by the U.S Food and Drug Adminstration.

* The brands listed are trademarks of their respective owners and are not trademarks of Cipla Ltd. The markers of these brands are not affiliated with and do not endorse Cipla Ltd. or its products.

Rev. 5/2015

CIPLA LTD.
Verna Indl. Estate,
Goa 403 722 India.

Unwinding Direction

Each capsule contains:
Lopinavir USP ..... 40 mg
Ritonavir USP ..... 10 mg

Usual Dosage: See medication guide for dosage and administration.

Do not use if safety seal under cap is broken or missing

Store Lopinavir and Ritonavir Oral Pellets below 30 °C (86 °F)

KEEP OUT OF REACH OF CHILDREN

Rx only

120 Capsules

Lopinavir and Ritonavir Oral Pellets

40 mg / 10 mg

Per Capsule

PHARMACIST:
Dispense the MEDICATION GUIDE with the drug product.

Cipla

Unvarnished Area for M.L., LOT, MFD. & EXP.

Directions for use:
Carefully open and sprinkle the contents of the prescribed number of capsules over sweetened porridge. The entire mixture should be swallowed immediately without chewing. After the child swallows the dose, administer a drink of water to ensure that no pellets are left behind in the child's mouth.

1

Mfd. by **CIPLA LTD.**
Verna Indl. Estate,
Goa 403 722 INDIA

JS64 A

Actual Size : 120 x 50 mm
Col.: PANTONE BRIGHT ORANGE C
Black
Pharmacode: 868_MINI
Date : 18-05-2015