HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KALETRA safely and effectively. See full prescribing information for KALETRA.

KALETRA (lopinavir/ritonavir) capsules, liquid filled for oral use
Initial U.S. Approval: 2000

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

Contraindications (4)	11/2016
Warnings and Precautions	11/2016
Diabetes Mellitus/Hyperglycemia (5.6)	

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

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

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

Capsules: Must be taken with food. (2)
Do not use once daily administration of KALETRA in:

- HIV-1 infected patients with three or more of the following lopinavir resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. (2.1)
- Combination with efavirenz, nevirapine, nelfinavir, carbamazepine, phenobarbital, or phenytoin. (2.1, 7.3)
- Pediatric patients. (2.2)

Adult Patients:

- 400/100 mg (three 133/33 mg capsules) twice daily
- or 800/200 mg (six 133/33 mg capsules) once daily in patients with less than three lopinavir resistance-associated substitutions. (2.1)

Pediatric Patients:

- Children less than 12 years of age who weigh greater than 40 kg or greater than 12 years of age: 400/100 mg twice daily (three 133/33 mg capsules) twice daily. (2.2)
- Children 14 days to 12 years of age who weigh less than 40 kg and in those children who cannot swallow capsules: Refer to the KALETRA oral solution full prescribing information for pediatric dosage and administration recommendations. (2.2)

Concomitant Therapy in Adults and Pediatric Patients:
Dose adjustments of KALETRA may be needed when co-administering with efavirenz, nevirapine, or nelfinavir. (2.1, 2.2)

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

- Capsules: 133.3 mg of lopinavir/33.3 mg of ritonavir. (3)

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

- Hypersensitivity to KALETRA (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, urticaria, angioedema) or any of its ingredients, including ritonavir. (4)
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated plasma levels may result in serious and/or life-threatening events. (4)
- Co-administration with potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross resistance. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------

The following have been observed in patients receiving KALETRA:

- The concomitant use of KALETRA 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)
- Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate. (5.2)
- 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. (5.3, 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, 5.4, 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, 5.5, 7, 12.3)
- Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.6), immune reconstitution syndrome (5.7), redistribution/accumulation of body fat. (5.9)
- Total cholesterol and triglycerides elevations. Monitor prior to therapy and periodically thereafter. (5.8)
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required. (5.10)

---------- **ADVERSE REACTIONS** ----------

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

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- **DRUG INTERACTIONS** ----------

Co-administration of KALETRA 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: 11/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Adult Patients
2.2 Pediatric Patients
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Risk of Serious Adverse Reactions Due to Drug Interactions
5.2 Pancreatitis
5.3 Hepatotoxicity
5.4 QT Interval Prolongation
5.5 PR Interval Prolongation
5.6 Diabetes Mellitus/Hyperglycemia
5.7 Immune Reconstitution Syndrome
5.8 Lipid Elevations
5.9 Fat Redistribution
5.10 Patients with Hemophilia
5.11 Resistance/Cross-resistance
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Potential for KALETRA to Affect Other Drugs
7.2 Potential for Other Drugs to Affect Lopinavir
7.3 Established and Other Potentially Significant Drug Interactions
7.4 Drugs with No Observed or Predicted Interactions with KALETRA
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES

14.1 Adult Patients without Prior Antiretroviral Therapy
14.2 Adult Patients with Prior Antiretroviral Therapy
14.3 Other Studies Supporting Approval in Adult Patients
14.4 Pediatric Studies
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

The following points should be considered when initiating therapy with KALETRA:

- The use of other active agents with KALETRA 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 KALETRA *[see Microbiology (12.4)]*. The number of baseline lopinavir resistance-associated substitutions affects the virologic response to KALETRA *[see Microbiology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

KALETRA capsules must be taken with food.

2.1 Adult Patients

- KALETRA capsules 400/100 mg (given as three 133/33 mg capsules) twice daily.
- KALETRA capsules 800/200 mg (given as six 133/33 mg capsules) once daily in patients with less than three lopinavir resistance-associated substitutions.

Once daily administration of KALETRA is not recommended for adult patients with three or more of the following lopinavir resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V *[see Microbiology (12.4)]*.

KALETRA should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin *[see Drug Interactions (7)]*.

<u>Concomitant therapy: Efavirenz, Nevirapine, or Nelfinavir</u>

[see Clinical Pharmacology (12.3) and *Drug Interactions (7.3)]*

KALETRA capsules should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, or nelfinavir.

- A dose increase is recommended for all patients who use KALETRA capsules. The recommended dose of KALETRA capsules is 533/133 mg twice daily (given as four 133/33 mg capsules twice daily taken with food) when used in combination with efavirenz, nevirapine, or nelfinavir.

2.2 Pediatric Patients

KALETRA capsules should not be administered once daily in pediatric patients less than 18 years of age.

For children less than 12 years of age who weigh greater than 40 kg or for children greater than 12 years of age, the maximum dose of 400/100 mg twice daily (given as three 133/33 mg capsules twice daily taken with food) is recommended.

The use of KALETRA oral solution is recommended for children 14 days to 12 years of age who weigh less than 40 kg and in those children who cannot swallow capsules. Please refer to the KALETRA oral solution full prescribing information for pediatric dosage and administration and other important information for these children.

Concomitant Therapy: Efavirenz, Nevirapine, or Nelfinavir

A dose increase is recommended for all pediatric patients who use KALETRA capsules. For children weighing more than 45 kg, the recommended dose of KALETRA capsules is 533/133 mg twice daily (given as four 133/33 mg capsules twice daily taken with food) when used in combination with efavirenz, nevirapine, or nelfinavir.

3 DOSAGE FORMS AND STRENGTHS

KALETRA (lopinavir/ritonavir) capsules are orange soft gelatin capsules imprinted with the "a" logo and the code PK. KALETRA is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules.

4 CONTRAINDICATIONS

- KALETRA 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.
- KALETRA 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. These drugs are listed in Table 1.
- KALETRA is contraindicated with drugs that are potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance.

Table 1. Drugs That are Contraindicated with KALETRA

Drug Class	Drugs within Class That are Contraindicated with KALETRA	Clinical Comments
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antiarrhythmic	Dronedarone	Potential for cardiac arrhythmias.
Anti-gout	Colchicine[a]	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antimycobacterial	Rifampin	May lead to loss of virologic response and possible

		resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents.
Antipsychotics	Lurasidone Pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot Derivatives	Dihydroergotamine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Hepatitis C direct acting antiviral	Elbasvir/grazoprevir	Potential for the increased risk of alanine transaminase (ALT) elevations.
Herbal Products	St. John's Wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
PDE5 Inhibitor	Sildenafil[b] (Revatio®) when used for the treatment of pulmonary arterial hypertension	Potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.
Sedative/Hypnotics	Triazolam; orally administered midazolam[c]	Prolonged or increased sedation or respiratory depression.

[a] see *Drug Interactions (7), Table 6* for colchicine doses in patients with normal hepatic and renal function.
[b] see *Drug Interactions (7), Table 6* for co-administration of sildenafil in patients with erectile dysfunction.
[c] see *Drug Interactions (7), Table 6* for parenterally administered midazolam.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of KALETRA, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving KALETRA, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of KALETRA, 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 KALETRA.
- Loss of therapeutic effect of KALETRA and possible development of resistance.

See Table 6 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 KALETRA therapy; review concomitant medications during KALETRA therapy, and monitor for the adverse reactions associated with the concomitant medications *[see Contraindications (4)* and *Drug Interactions (7)]*.

5.2 Pancreatitis

Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations are a risk factor for development of pancreatitis *[see Warnings and Precautions (5.8)]*. 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 KALETRA 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 KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.

5.3 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 KALETRA.

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 KALETRA therapy has not been established.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as early as 7 days after the initiation of KALETRA in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with KALETRA therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with KALETRA 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 KALETRA treatment *[see Use in Specific Populations (8.6)]*.

5.4 QT Interval Prolongation

Postmarketing cases of QT interval prolongation and torsade de pointes have been reported although causality of KALETRA 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)]*.

5.5 PR Interval Prolongation

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

The impact on the PR interval of co-administration of KALETRA 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 KALETRA with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended *[see Drug Interactions (7),* and *Clinical Pharmacology (12.3)]*.

5.6 Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-1 infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. Consider monitoring for hyperglycemia, new onset diabetes mellitus or an exacerbation of diabetes mellitus in patients treated with KALETRA.

5.7 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including KALETRA. 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.

5.8 Lipid Elevations

Treatment with KALETRA 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 KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with KALETRA and HMG-CoA reductase inhibitors *[see Contraindications (4), Drug Interactions (7.3),* and *Clinical Pharmacology (12.3)]*.

5.9 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.

5.10 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.

5.11 Resistance/Cross-resistance

Because the potential for HIV-1 cross-resistance among protease inhibitors has not been fully explored in treatment-naïve patients, it is unknown what effect therapy with KALETRA 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 (5.4, 5.5)]*
- Drug Interactions *[see Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7),* and *Clinical Pharmacology (12.3)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3),* and *Use in Specific Populations (8.6)]*

6.1 Clinical Trials Experience

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

<u>Adverse Reactions in Adults</u>

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

In clinical studies the incidence of diarrhea in patients treated with either KALETRA 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 Kaletra capsules

or tablets. At the time of treatment discontinuation, 4.2-6.3% of patients taking once daily Kaletra and 1.8-3.7% of those taking twice daily Kaletra reported ongoing diarrhea.

Commonly reported adverse reactions to KALETRA 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 in Adults

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 greater than or equal to 2% of Adult Antiretroviral-Naïve Patients

		Study 863 (48 Weeks)		Study 720 (360 Weeks)	Study 418 (48 weeks)		Study 730 (48 Weeks)	
Variable	**Limit[1]**	**KALETRA 400/100 mg Twice Daily + d4T +3TC (N = 326)**	**Nelfinavir 750 mg Three Times Daily + d4T + 3TC (N = 327)**	**KALETRA Twice Daily + d4T + 3TC (N = 100)**	**KALETRA 800/200 mg Once Daily + TDF + FTC (N=115)**	**KALETRA 400/100 mg Twice Daily + TDF + FTC (N=75)**	**KALETRA Once Daily + TDF +FTC (N=333)**	**KALETRA Twice Daily + TDF +FTC (N=331)**

Chemistry	**High**							
Glucose	> 250 mg/dL	2%	2%	4%	3%	1%	0%	<1%
Uric Acid	> 12 mg/dL	2%	2%	5%	0%	3%	<1%	1%
SGOT/ AST[2]	> 180 U/L	2%	4%	10%	5%	3%	1%	2%
SGPT/ ALT[2]	>215 U/L	4%	4%	11%	4%	3%	1%	1%
GGT	>300 U/L	N/A	N/A	10%	N/A	N/A	N/A	N/A
Total Cholesterol	>300 mg/dL	9%	5%	27%	3%	3%	4%	3%
Triglycerides	>750 mg/dL	9%	1%	29%	5%	4%	3%	6%
Amylase	>2 x ULN	3%	2%	4%	7%	5%	N/A	N/A
Lipase	>2 x ULN	N/A	N/A	N/A	N/A	N/A	3%	5%
Chemistry	**Low**							
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	N/A	N/A	2%	2%
Hematology	**Low**							
Neutrophils	<0.75 x 10^9/L	1%	3%	5%	5%	1%	2%	1%

1 ULN = upper limit of the normal range; N/A = Not Applicable.
2 Criterion for Study 730 was >5x ULN (AST/ALT).

Table 4. Grade 3-4 Laboratory Abnormalities Reported in greater than or equal to 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]**	**KALETRA 400/100 mg Twice Daily + NVP + NRTIs**	**Investigator-Selected Protease Inhibitor(s) + NVP + NRTIs**	**KALETRA Twice Daily + NNRTI + NRTIs (N = 127)**	**KALETRA 800/200 mg Once Daily +NRTIs (N=300)**	**KALETRA 400/100 mg Twice Daily +NRTIs (N=299)**

		(N = 148)	(N = 140)			
Chemistry	**High**					
Glucose	>250 mg/dL	1%	2%	5%	2%	2%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%	1%	1%
SGOT/AST[4]	>180 U/L	5%	11%	8%	3%	2%
SGPT/ALT[4]	>215 U/L	6%	13%	10%	2%	2%
GGT	>300 U/L	N/A	N/A	29%	N/A	N/A
Total Cholesterol	>300 mg/dL	20%	21%	39%	6%	7%
Triglycerides	>750 mg/dL	25%	21%	36%	5%	6%
Amylase	>2 x ULN	4%	8%	8%	4%	4%
Lipase	>2 x ULN	N/A	N/A	N/A	4%	1%
Creatine Phosphokinase	>4 x ULN	N/A	N/A	N/A	4%	5%
Chemistry	**Low**					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	3%	3%
Inorganic Phosphorus	<1.5 mg/dL	1%	0%	2%	1%	<1%
Hematology	**Low**					
Neutrophils	<0.75 x 10^9/L	1%	2%	4%	3%	4%
Hemoglobin	<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 KALETRA 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 KALETRA in combination with NRTIs and nevirapine.
4 Criterion for Study 802 was >5x ULN (AST/ALT).

Adverse Reactions in Pediatric Patients

KALETRA oral solution dosed up to 300/75 mg per 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).

KALETRA oral solution and soft gelatin capsules dosed at higher than recommended doses including 400/100 mg per m^2 (without concomitant NNRTI) and 480/120 mg per 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 in Pediatric Patients

The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 5.

Table 5. Grade 3-4 Laboratory Abnormalities Reported in greater than or equal to 2% Pediatric Patients in Study 940

Variable	**Limit[1]**	**KALETRA 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.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postmarketing use of KALETRA. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to KALETRA exposure.

Body as a Whole

Redistribution/accumulation of body fat has been reported *[see Warnings and Precautions (5.9)]*.

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 (5.4, 5.5)]*.

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 KALETRA 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 KALETRA. Thus, co-administration of KALETRA 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 6.

Additionally, KALETRA induces glucuronidation.

Published data suggest that lopinavir is an inhibitor of OATP1B1.

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

7.3 Established and Other Potentially Significant Drug Interactions

Table 6 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 6. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
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 KALETRA 400/100 mg twice daily. KALETRA once daily has not been studied in combination with indinavir.
HIV-1 Protease Inhibitor: nelfinavir*	↑ nelfinavir ↑ M8 metabolite of nelfinavir ↓ lopinavir	Increase KALETRA dose to 533/133 mg and decrease nelfinavir dose to 1000 mg twice daily, when co-administered. KALETRA once-daily in combination with nelfinavir is not recommended *[see Dosage and Administration (2.1)]*.
HIV-1 Protease Inhibitor: ritonavir*	↑ lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: saquinavir	↑ saquinavir	The saquinavir dose is 1000 mg twice daily (with no additional ritonavir), when co-administered with KALETRA 400/100 mg twice daily. KALETRA once daily has not been studied in combination with saquinavir.
HIV-1 Protease Inhibitor: tipranavir*	↓ lopinavir	Co-administration with tipranavir (500 mg twice daily) and ritonavir (200 mg twice daily) is not recommended.
HIV CCR5 – Antagonist: maraviroc*	↑ maraviroc	When co-administered, patients should receive 150 mg twice daily of maraviroc. For further details see complete prescribing information for maraviroc.
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ lopinavir	Increase the dose of KALETRA capsules to 533/133 mg when KALETRA capsule is co-administered with efavirenz or nevirapine. KALETRA once daily in combination with efavirenz or nevirapine is not recommended *[see Dosage and Administration (2.1)]*.
Non-nucleoside Reverse Transcriptase Inhibitor:	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been

delavirdine		established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA capsules (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir disoproxil fumarate*	↑ tenofovir	Patients receiving KALETRA and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside Reverse Transcriptase Inhibitors: abacavir, zidovudine	↓ abacavir ↓ zidovudine	The clinical significance of this potential interaction is unknown.
Other Agents		
Antiarrhythmics: e.g. amiodarone, bepridil, lidocaine (systemic), quinidine	↑ antiarrhythmics	For contraindicated antiarrhythmics, *see Contraindications (4).* Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with KALETRA.
Anticancer Agents: vincristine, vinblastine, dasatinib, nilotinib	↑ anticancer agents	For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when KALETRA 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 KALETRA. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.

Anticoagulants: warfarin, rivaroxaban	 ↑↓ warfarin ↑ rivaroxaban	Concentrations of warfarin may be affected. Initial frequent monitoring of the INR during KALETRA and warfarin co-administration is recommended. Avoid concomitant use of rivaroxaban and KALETRA. Co-administration of KALETRA and rivaroxaban may lead to increased risk of bleeding.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ lopinavir ↓ phenytoin	KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly and should be used with caution. KALETRA once daily in combination with carbamazepine, phenobarbital, or phenytoin is not recommended. In addition, co-administration of phenytoin and KALETRA may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with KALETRA.
Anticonvulsants: lamotrigine, valproate	↓ lamotrigine ↓ or ↔ valproate	A dose increase of the lamotrigine or valproate may be needed when co-administered with KALETRA and therapeutic concentration monitoring for lamotrigine may be indicated; particularly during dosage adjustments.
Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Patients receiving KALETRA and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	For patients with renal impairment adjust clarithromycin dose as follows: • For patients on KALETRA with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients on KALETRA 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	High doses of ketoconazole (> 200 mg/day) or

ketoconazole*, itraconazole, voriconazole isavuconazonium sulfate*	↑ itraconazole ↓ voriconazole ↑isavuconazonium	itraconazole (> 200 mg/day) are not recommended. The coadministration of voriconazole and KALETRA should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Isavuconazonium and Kaletra should be coadministered with caution. Alternative antifungal therapies should be considered in these patients.
Anti-gout: colchicine	↑ colchicine	Concomitant administration with colchicine is contraindicated in patients with renal and/or hepatic impairment *[see Contraindications (4)]*. <u>For patients with normal renal or hepatic function:</u> *Treatment of gout flares-co-administration of colchicine in patients on KALETRA:* 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. *Prophylaxis of gout flares-co-administration of colchicine in patients on KALETRA:* 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 KALETRA:* Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: bedaquiline	↑ bedaquiline	For contraindicated antimycobacterials, *[see Contraindications (4)]*. Bedaquiline should only be used with

		KALETRA if the benefit of co-administration outweighs the risk.
Antimycobacterial: rifabutin*	↑ rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg per day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse reactions is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Antipsychotics: quetiapine	↑ quetiapine	Initiation of KALETRA 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 KALETRA: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Sedative/hypnotics: parenterally administered midazolam	↑ midazolam	For contraindicated sedative/hypnotics, *[see Contraindications (4)]*. If KALETRA is co-administered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
Contraceptive: ethinyl estradiol*	↓ ethinyl estradiol	Because contraceptive steroid concentrations may be altered when KALETRA is co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.
Corticosteroids (systemic): e.g. budesonide, dexamethasone, prednisone	↓ lopinavir ↑ glucocorticoids	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly. Concomitant use of glucocorticoids that are metabolized by CYP3A, particularly for long-

		term use, should consider the potential benefit of treatment versus the risk of systemic corticosteroid effects. Concomitant use may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.
Dihydropyridine Calcium Channel Blockers: e.g. felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Clinical monitoring of patients is recommended and a dose reduction of the dihydropyridine calcium channel blocker may be considered.
Endothelin Receptor Antagonists: bosentan	↑ bosentan	<u>Co-administration of bosentan in patients on KALETRA:</u> In patients who have been receiving KALETRA 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 KALETRA in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of KALETRA. After at least 10 days following the initiation of KALETRA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Hepatitis C direct acting antiviral: boceprevir* simeprevir* ombitasvir/parataprevir/ ritonavir and dasabuvir*	↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ simeprevir ↑ ombitsavir ↑ parataprevir ↑ ritonavir ↔ dasabuvir	For contraindicated hepatitis C direct acting antivirals, *[see Contraindications (4)]*. It is not recommended to co-administer KALETRA and boceprevir, simeprevir, or ombitasvir/parataprevir/ritonavir and dasabuvir.
HMG-CoA Reductase Inhibitors: atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	For contraindicated HMG-CoA reductase inhibitors, *[see Contraindications (4)]*. Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg per day.

Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Inhaled or Intranasal Steroids: e.g. fluticasone, budesonide	↑ glucocorticoids	Concomitant use of KALETRA and fluticasone or other glucocorticoids that are metabolized by CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use may result in increased steroid concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients when certain ritonavir-containing products have been co-administered with fluticasone propionate or budesonide.
Long-acting Beta-Adrenoceptor Agonist: salmeterol	↑ salmeterol	Concurrent administration of salmeterol and KALETRA is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Narcotic Analgesics: methadone*, fentanyl	↓ methadone ↑ fentanyl	Dosage of methadone may need to be increased when co-administered with KALETRA. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with KALETRA.
PDE5 Inhibitors: avanafil, sildenafil, tadalafil, vardenafil	↑ avanafil ↑ sildenafil ↑ tadalafil ↑ vardenafil	For contraindicated PDE5 inhibitors, *[see Contraindications (4)]*. Do not use KALETRA with avanafil because a safe and effective avanafil dosage regimen has not been established. Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving KALETRA. Co-administration of KALETRA 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 *[see Contraindications (4)]*. The following dose adjustments are recommended for use of tadalafil (Adcirca®) with KALETRA: Co-administration of ADCIRCA in patients on KALETRA: In patients receiving KALETRA for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Co-administration of KALETRA in patients on ADCIRCA: Avoid use of ADCIRCA during the initiation of KALETRA. Stop ADCIRCA at least 24 hours prior to starting KALETRA. After at least one week following the initiation of KALETRA, 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 KALETRA

Drug interaction or clinical studies reveal no clinically significant interaction between KALETRA and desipramine (CYP2D6 probe), etravirine, pitavastatin, pravastatin, stavudine, lamivudine, omeprazole, raltegravir, ranitidine , or rilpivirine.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Human Data:

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

Antiretroviral Pregnancy Registry: As of January 2011, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 2458 exposures to lopinavir containing regimens (738 exposed in the first trimester and 1720 exposed in the second and third trimester). Birth defects occurred in 16 of the 738 (2.2%) live births (first trimester exposure) and 41 of the 1720 (2.4%) live births (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between lopinavir and overall birth defects observed in the APR.

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 KALETRA.

8.4 Pediatric Use

The safety, efficacy, and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 14 days have not been established. KALETRA should not be administered once daily in pediatric patients. The KALETRA Oral Solution full prescribing information should be consulted for information for young children who cannot swallow KALETRA Capsules.

An open-label, multi-center, dose-finding trial was performed to evaluate the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg per mL and ritonavir 20 mg per mL at a dose of 300/75 mg per m^2 twice daily plus two NRTIs in HIV-infected infants at least 14 days and less than 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 less than 400 copies per mL at Week 24 *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3),* and *Clinical Studies (14.4)]*.

Safety and efficacy in pediatric patients 6 months of age and older 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 KALETRA oral solution containing lopinavir 80 mg per mL and ritonavir 20 mg per 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 per m^2 oral solution twice daily regimen without nevirapine and the 300/75 mg per 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),* and *Clinical Studies (14.4)]*.

A prospective multicenter, open-label trial evaluated the pharmacokinetic profile, tolerability, safety and efficacy of high-dose KALETRA with or without concurrent NNRTI therapy (Group 1: 400/100 mg per m^2 twice daily plus 2 or more NRTIs; Group 2: 480/120 mg per m^2 twice daily plus 1 or more NRTIs plus 1 NNRTI) in 26 children and adolescents at least 2 years to less than 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 KALETRA could overcome protease inhibitor cross-resistance. High doses of KALETRA 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 less than 400 copies per 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),* and *Clinical Pharmacology (12.3)]*.

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

8.5 Geriatric Use

Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly

patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

KALETRA 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 (5.3)* and *Clinical Pharmacology (12.3)]*.

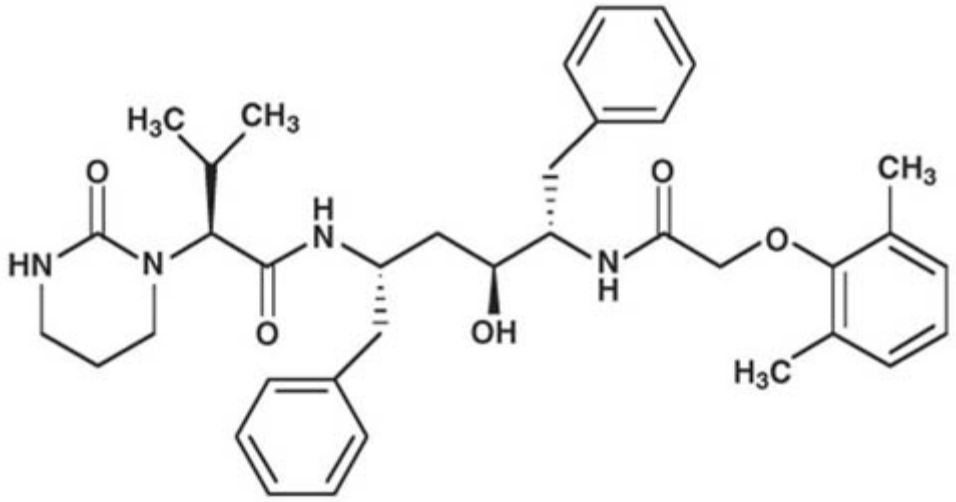
10 OVERDOSAGE

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

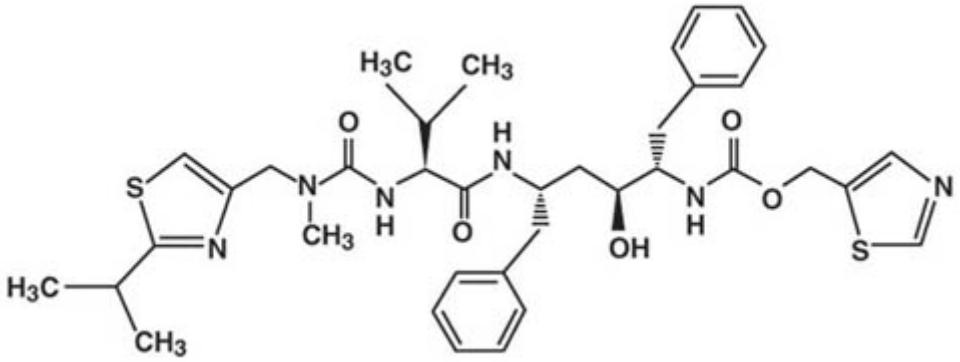
11 DESCRIPTION

KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 protease. As co-formulated in KALETRA, 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:



KALETRA capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

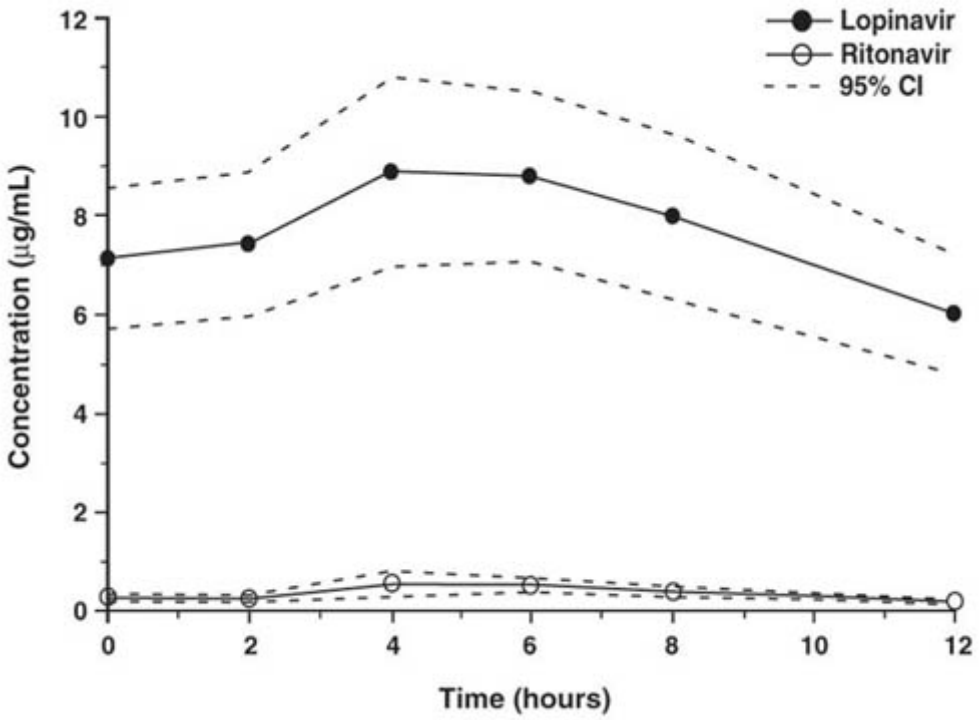
Lopinavir is an antiviral drug *[see Microbiology (12.4)]*. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

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 KALETRA 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 KALETRA is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 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 KALETRA twice daily with food for 3 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 µg per mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 µg per mL and minimum concentration within a dosing interval was 5.5 ± 2.7 µg per mL.

Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 µg•h per 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 KALETRA 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 KALETRA oral solution relative to the capsule formulation.

Effects of Food on Oral Absorption

Administration of a single 400/100 mg dose of KALETRA capsules with a moderate fat meal (500-682 kcal, 23 to 25% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max}, respectively, relative to fasting. Relative to fasting, administration of KALETRA capsules with a high fat meal (872 kcal, 56% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively. To enhance bioavailability and minimize pharmacokinetic variability KALETRA capsules should be taken with food.

Distribution

At steady state, lopinavir is approximately 98-99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg KALETRA 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 KALETRA 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 per hr (mean ± SD, n = 19).

Once Daily Dosing

The pharmacokinetics of once daily KALETRA have been evaluated in HIV-1 infected subjects naïve to antiretroviral treatment. KALETRA 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 KALETRA 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 per 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 per mL and minimum concentration within a dosing interval was 1.7 ± 1.6 µg per mL. Lopinavir AUC over a 24 hour dosing interval averaged 154.1 ± 61.4 µg•h per mL.

The pharmacokinetics of once daily KALETRA has also been evaluated in treatment experienced HIV-1 infected subjects. Lopinavir exposure (C_{max}, $AUC_{[0-24h]}$, C_{trough}) with once daily KALETRA 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 KALETRA, respectively. KALETRA 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 KALETRA doses at steady state.

PR interval prolongation was also noted in subjects receiving KALETRA 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 KALETRA, respectively *[see Warnings and Precautions (5.4, 5.5)]*.

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 KALETRA soft gelatin capsule and oral solution (Group 1: 400/100 mg per m^2 twice daily plus 2 NRTIs; Group 2: 480/120 mg per m^2 twice daily plus at least 1 NRTI plus 1 NNRTI) have been evaluated in children and adolescents at least 2 years to less than 18 years of age who had failed prior therapy (n=26) in Study 1038. KALETRA doses of 400/100 and 480/120 mg per m^2 resulted in high lopinavir exposure, as almost all subjects had lopinavir AUC_{12} above 100 µg•h per mL. Both groups of subjects also achieved relatively high average minimum lopinavir concentrations.

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 KALETRA 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 KALETRA to subjects with hepatic impairment. KALETRA has not been studied in patients with severe hepatic impairment *[see Warnings and Precautions (5.3)* and *Use in Specific Populations (8.6)]*.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of KALETRA 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), Warnings and Precautions (5)* and *Drug Interactions (7)]*.

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

KALETRA 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.

KALETRA 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 KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with KALETRA and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in Table 7 (effect of other drugs on lopinavir) and Table 8 (effect of KALETRA 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 6 in *Drug Interactions (7)*.

Table 7. 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 KALETRA (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 bedtime, 9 d	400/100 capsule twice daily, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 at bedtime, 9 d	500/125 tablet twice daily, 10 d	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 at bedtime, 9 d	600/150 tablet twice daily, 10 d	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Elbasvir/ grazoprevir[14]	50 once daily, 7 d	400/100 twice daily, 21d	9	1.02 (0.92, 1.13)	1.02 (0.93, 1.13)	1.07 (0.97, 1.18)
	200 once daily, 7 d		13	0.97 (0.88, 1.08)	1.03 (0.96, 1.16)	0.97 (0.81, 1.15)
Etravirine	200 twice daily	400/100 twice day (tablets)	16	0.89 (0.82-0.96)	0.87 (0.83-0.92)	0.80 (0.73-0.88)
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)

Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir	25/150/100 + dasabuvir 400, 28 d	400/100 tablet twice daily, 14 d	6	0.87 (0.76, 0.99)	0.94 (0.81, 1.10)	1.15 (0.93, 1.42)
Omeprazole	40 once daily, 5 d	400/100 tablet twice daily, 10 d	12	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)
	40 once daily, 5 d	800/200 tablet once daily, 10 d	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
Pitavastatin[6]	4 once daily, 5 d	400/100 tablet twice daily, 16 d	23	0.93 (0.88, 0.98)	0.91 (0.86, 0.97)	N/A
Pravastatin	20 once daily, 4 d	400/100 capsule twice daily, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 once daily, 10 d	400/100 capsule twice daily, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Ranitidine	150 single dose	400/100 tablet twice daily, 10 d	12	0.99 (0.95, 1.03)	0.97 (0.93, 1.01)	0.90 (0.85, 0.95)
	150 single dose	800/200 tablet once daily, 10 d	10	0.97 (0.95, 1.00)	0.95 (0.91, 0.99)	0.82 (0.74, 0.91)
Rifampin	600 once daily, 10 d	400/100 capsule twice daily, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 once daily, 14 d	800/200 capsule twice daily, 9 d[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)
Rilpivirine	150 once daily[13]	400/100 twice daily (capsules)	15	0.96 (0.88-1.05)	0.99 (0.89-1.10)	0.89 (0.73-1.08)
Ritonavir[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)
Tenofovir disoproxil fumarate[9]	300 once daily, 14 d	400/100 capsule twice daily, 14 d	24	NC[†]	NC[†]	NC[†]

Tipranavir/ ritonavir[4]	500/200 twice daily (28 doses)[#]	400/100 capsule twice daily (27 doses)	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 This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the co-administered drug.
14 Data extracted from the elbasvir/grazoprevir package insert.
* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.
N/A = Not available.
† NC = No change.
# For the nevirapine 200 mg twice daily study, ritonavir, and tipranavir/ritonavir studies, KALETRA was administered with or without food. For all other studies, KALETRA was administered with food.

Table 8. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA for Recommended Alterations in Dose or Regimen

Co-administered Drug	**Dose of Co-administered Drug (mg)**	**Dose of KALETRA (mg)**	**n**	**Ratio (in combination with KALETRA/alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00**		
				C_{max}	**AUC**	**C_{min}**
Bedaquiline[1]	400 single dose	400/100 twice daily, 24 d	N/A	N/A	1.22 (1.11, 1.34)	N/A

Boceprevir	800 q8h, 6 d	400/100 tablet twice daily, 22 d	13[9]	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 bedtime, 9 d	400/100 capsule twice daily, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Elbasvir/ grazoprevir[11]	50 once daily, 7 d	400/100 twice daily, 21d	10	2.87 (2.29, 3.58)	3.71 (3.05, 4.53)	4.58 (3.72, 5.64)
	200 once daily, 7 d		13	7.31 (5.65, 9.45)	12.86 (10.25, 16.13)	21.70 (12.99, 36.25)
Ethinyl Estradiol	35 µg once daily, 21 d (Ortho Novum®)	400/100 capsule twice daily, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Etravirine	200 twice daily	400/100 twice day (tablets)	16	0.70 (0.64-0.78)	0.65 (0.59-0.71)	0.55 (0.49-0.62)
Fosamprenavir[3]	700 twice daily plus ritonavir 100 twice daily, 14 d	400/100 capsule twice daily, 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir[4]	600 twice daily, 10 d combo nonfasting vs. 800 three times daily, 5 d alone fasting	400/100 capsule twice daily, 15 d	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 capsule twice daily, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Maraviroc[13]	300 twice daily	400/100 twice daily	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)
Methadone	5 single dose	400/100 capsule twice daily, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A

Nelfinavir[4]	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)
Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir	25/150/100 + dasabuvir 400, 28 d	400/100 tablet twice daily, 14 d	6	1.14 (1.01, 1.28)	1.17 (1.07, 1.28)	1.24 (1.14, 1.34)
				2.04 (1.30, 3.20)	2.17 (1.63, 2.89)	2.36 (1.00, 5.55)
				1.55 (1.16, 2.09)	2.05 (1.49, 2.81)	5.25 (3.33, 8.28)
				0.99 (0.75, 1.31)	0.93 (0.75, 1.15)	0.68 (0.57, 0.80)
Pitavastatin[5]	4 once daily, 5 d	400/100 tablet twice daily, 16 d	23	0.96 (0.84, 1.10)	0.80 (0.73, 0.87)	N/A
Pravastatin	20 once daily, 4 d	400/100 capsule twice daily, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	150 once daily, 10 d; combo vs. 300 once daily, 10 d; alone	400/100 capsule twice daily, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-*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[6]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)

Rilpivirine	150 once daily[10]	400/100 twice daily (capsules)	15	1.29 (1.18-1.40)	1.52 (1.36-1.70)	1.74 (1.46-2.08)
Rosuvastatin[7]	20 once daily, 7 d	400/100 tablet twice daily, 7 d	15	4.66 (3.4, 6.4)	2.08 (1.66, 2.6)	1.04 (0.9, 1.2)
Tenofovir alafenamide[12]	10 once daily	800/200 tablet once daily	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	N/A
Tenofovir disoproxil fumarate[8]	300 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 Data extracted from the bedaquiline package insert.
2 Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.
3 Data extracted from the fosamprenavir package insert.
4 Ratio of parameters for indinavir, and nelfinavir are not normalized for dose.
5 Data extracted from the pitavastatin package insert and results presented at the 2011 International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (Morgan*, et al, poster #MOPE170*).
6 Effect on the dose-normalized sum of rifabutin parent and 25-*O*-desacetyl rifabutin active metabolite.
7 Kiser, et al. J Acquir Immune Defic Syndr. 2008 Apr 15;47(5):570-8.
8 Data extracted from the tenofovir package insert.
9 N=12 for C_{min} (test arm)
10 This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the co-administered drug.
11 Data extracted from the elbasvir/grazoprevir package insert
12 Data extracted from the tenofovir alafenamide/emtricitabine package insert
13 Data extracted from the maraviroc package insert
* Parallel group design; n for KALETRA + 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 10-27

nM (0.006-0.017 µg per mL, 1 µg per mL = 1.6 µM) and ranged from 4-11 nM (0.003-0.007 µg per 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 65-289 nM (0.04-0.18 µg per 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 12-180 nM (0.008-113 µg per 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 KALETRA 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 greater than 400 copies per mL at Week 24, 32, 40 and/or 48 were analyzed. No evidence of resistance to KALETRA was observed in 37 evaluable KALETRA-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 KALETRA in antiretroviral treatment naïve pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

Resistance to KALETRA has been noted to emerge in patients treated with other protease inhibitors prior to KALETRA therapy. In studies of 227 antiretroviral treatment naïve (100) and protease inhibitor experienced (127) patients, isolates from 4 of 23 patients with quantifiable (greater than 400 copies per mL) viral RNA following treatment with KALETRA 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 KALETRA therapy. Following viral rebound, isolates from these patients all contained additional substitutions, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify patterns of lopinavir resistance-associated substitutions in isolates from patients on KALETRA 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 KALETRA 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 greater than 4-fold reduced susceptibility to nelfinavir (n = 13) and saquinavir (n = 4), displayed less than 4-fold reduced susceptibility to lopinavir. Isolates with greater than 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 KALETRA 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 KALETRA therapy in treatment-experienced patients, with respect to baseline viral genotype in three studies and baseline viral phenotype in one study.

Virologic response to KALETRA 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 9 shows the 48-week virologic response (HIV-1 RNA less than 400 copies per 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 KALETRA for adult patients with three or more of the above substitutions is not recommended.

Table 9. Virologic Response (HIV-1 RNA <400 copies/mL) at Week 48 by Baseline KALETRA Susceptibility and by Number of Protease Substitutions Associated with Reduced Response to KALETRA[1]

Number of protease inhibitor substitutions at baseline[1]	Study 888 (Single protease inhibitor-experienced[2], NNRTI-naïve) n=130	Study 765 (Single protease inhibitor-experienced[3], NNRTI-naïve) n=56	Study 957 (Multiple protease inhibitor-experienced[4], NNRTI-naïve) n=50
0-2	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 KALETRA 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 greater than 1,000 copies per 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 KALETRA 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 greater than 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 10.

Table 10. 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 1.6-2.2 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 KALETRA 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 KALETRA 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 KALETRA 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 per kg per 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: KALETRA Capsules twice daily plus stavudine plus lamivudine compared to nelfinavir three times daily plus stavudine plus lamivudine

Study 863 was a randomized, double-blind, multicenter trial comparing treatment with KALETRA 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 per mm^3 (range: 2 to 949 cells per mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies per mL (range: 2.6 to 6.8 log_{10} copies per mL).

Treatment response and outcomes of randomized treatment are presented in Table 11.

Table 11. Outcomes of Randomized Treatment Through Week 48 (Study 863)

Outcome	KALETRA+d4T+3TC (N = 326)	Nelfinavir+d4T+3TC (N = 327)
Responder[1]	75%	62%
Virologic failure[2] Rebound Never suppressed through Week 48	9% 7% 2%	25% 15% 9%
Death	2%	1%
Discontinued due to adverse events	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 KALETRA arm and 24% in the nelfinavir arm.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV-1 RNA less than 400 copies per mL (75% vs. 62%, respectively) and HIV-1 RNA less than 50 copies per mL (67% vs. 52%, respectively). Treatment response by baseline HIV-1 RNA level subgroups is presented in Table 12.

Table 12. Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)

Baseline Viral Load (HIV-1 RNA copies/mL)	KALETRA +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 per mm^3 for the KALETRA arm and 195 cells per mm^3 for the nelfinavir arm.

Study 418: KALETRA Capsules once-daily plus tenofovir DF plus emtricitabine compared to KALETRA Capsules twice-daily plus tenofovir DF plus emtricitabine

Study 418 is an ongoing, randomized, open-label, multicenter trial comparing treatment with KALETRA 800/200 mg once-daily plus tenofovir DF and emtricitabine versus KALETRA 400/100 mg twice-daily plus tenofovir DF and emtricitabine in 190 antiretroviral treatment-naïve patients. Patients had a mean age of 39 years (range: 19 to 75), 54% were Caucasian, and 78% were male. Mean baseline CD_4 cell count was 260 cells per mm^3 (range: 3 to 1006 cells per mm^3) and mean baseline plasma HIV-1 RNA was 4.8 log_{10} copies per mL (range: 2.6 to 6.4 log_{10} copies per mL).

Treatment response and outcomes of randomized treatment are presented in Table 13.

Table 13. Outcomes of Randomized Treatment Through Week 48 (Study 418)

Outcome	KALETRA Once Daily + TDF + FTC (n = 115)	KALETRA Twice Daily + TDF + FTC (n = 75)
Responder[1]	71%	65%
Virologic failure[2]	10%	9%
Rebound	6%	5%
Never suppressed through Week 48	3%	4%
Death	0%	1%
Discontinued due to an adverse event	12%	7%
Discontinued for other reasons[3]	7%	17%

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, 71% in the KALETRA once-daily arm and 65% in the KALETRA twice-daily arm achieved and maintained HIV-1 RNA less than 50 copies per mL (95% confidence interval for the difference, -7.6% to 19.5%). Mean CD_4 cell count increases at Week

48 were 185 cells per mm^3 for the KALETRA once-daily arm and 196 cells per mm^3 for the KALETRA twice-daily arm.

Study 730: KALETRA Tablets once daily plus tenofovir DF plus emtricitabine compared to KALETRA Tablets twice daily plus tenofovir DF plus emtricitabine

Study 730 was a randomized, open-label, multicenter trial comparing treatment with KALETRA 800/200 mg once daily plus tenofovir DF and emtricitabine versus KALETRA 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 KALETRA 800/200 mg once daily (n = 333) or KALETRA 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 per mm^3 (range: 20 to 775 cells per mm^3) and mean baseline plasma HIV-1 RNA was 5.0 log_{10} copies per mL (range: 1.7 to 7.0 log_{10} copies per 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	**KALETRA Once Daily + TDF + FTC (n = 333)**	**KALETRA Twice Daily + TDF + FTC (n = 331)**
Responder[1]	78%	77%
Virologic failure[2] Rebound Never suppressed through Week 48	10% 5% 5%	8% 5% 3%
Death	1%	<1%
Discontinued due to adverse events	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 KALETRA once daily arm and 77% in the KALETRA twice daily arm achieved and maintained HIV-1 RNA less than 50 copies per mL (95% confidence interval for the difference, -5.9% to 6.8%). Mean CD4+ cell count increases at Week 48 were 186 cells per mm^3 for the KALETRA once daily arm and 198 cells per mm^3 for the KALETRA twice daily arm.

14.2 Adult Patients with Prior Antiretroviral Therapy

Study 888: KALETRA Capsules twice daily plus nevirapine plus NRTIs compared to investigator-selected protease inhibitor(s) plus nevirapine plus NRTIs

Study 888 was a randomized, open-label, multicenter trial comparing treatment with KALETRA capsules (400/100 mg twice daily) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naïve patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD4+ cell count was 322 cells per mm^3 (range: 10 to 1059 cells per mm^3) and mean baseline plasma HIV-1 RNA was 4.1 log_{10} copies per mL (range: 2.6 to 6.0 log_{10} copies per 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	KALETRA + nevirapine + NRTIs (n = 148)	Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n = 140)
Responder[1]	57%	33%
Virologic failure[2] Rebound Never suppressed through Week 48	24% 11% 13%	41% 19% 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 KALETRA arm compared to the investigator-selected protease inhibitor(s) arm with HIV-1 RNA less than 400 copies per mL (57% vs. 33%, respectively).

Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 111 cells per mm^3 for the KALETRA arm and 112 cells per mm^3 for the investigator-selected protease inhibitor(s) arm.

Study 802: KALETRA 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 KALETRA tablets in 599 subjects with detectable viral loads while receiving their current antiviral therapy. Of the enrolled subjects, 55% on both treatment arms had not been previously treated with a protease inhibitor and 81 – 88% had received prior NNRTIs as part of their anti-HIV treatment regimen. Patients were randomized in a 1:1 ratio to receive either KALETRA 800/200 mg once daily (n = 300) or KALETRA 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 per mm^3 (range: 4 to 952 cells per mm^3) and mean baseline plasma HIV-1 RNA was 4.3 log_{10} copies per mL (range: 1.7 to 6.6 log_{10} copies per 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	**KALETRA Once Daily + NRTIs (n = 300)**	**KALETRA 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 per mm^3 for the once daily group and 122 cells per mm^3 for the twice daily group.

14.3 Other Studies Supporting Approval in Adult Patients

Study 720: KALETRA twice daily plus stavudine plus lamivudine

Study 765: KALETRA twice daily plus nevirapine plus 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 KALETRA at up to three dose levels (200/100 mg twice daily [720 only], 400/100 mg twice daily, and 400/200 mg twice daily). In Study 720, all patients switched to 400/100 mg

twice daily between Weeks 48-72. Patients in study 720 had a mean age of 35 years, 70% were Caucasian, and 96% were male, while patients in study 765 had a mean age of 40 years, 73% were Caucasian, and 90% were male. Mean (range) baseline CD4+ cell counts for patients in study 720 and study 765 were 338 (3-918) and 372 (72-807) cells per 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 per mL, respectively.

Through 360 weeks of treatment in study 720, the proportion of patients with HIV-1 RNA less than 400 (less than 50) copies per 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 per 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 less than 400 (less than 50) copies per mL was 54% (50%) [n = 70], and the corresponding mean increase in CD4+ cell count was 212 cells per 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

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 KALETRA oral solution containing lopinavir 80 mg per mL and ritonavir 20 mg per 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 per mm^3 and mean baseline plasma HIV-1 RNA was 4.7 log_{10} copies per mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV-1 RNA less than 400 copies per 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 per mm^3 for antiretroviral naïve and 284 cells per 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 6 months to 12 years of age, the 230/57.5 mg per m^2 oral solution twice daily regimen without nevirapine and the 300/75 mg per 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 less than 400 copies per mL) similar to that seen in the adult clinical trials.

- Among patients 12 to 18 years of age receiving 400/100 mg per m^2 or 480/120 mg per m^2 (with efavirenz) twice daily, plasma concentrations were 60-100% higher than among 6 to 12 year old patients receiving 230/57.5 mg per 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 patient's prescribed lopinavir dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

KALETRA (lopinavir/ritonavir) capsules are orange soft gelatin capsules imprinted with the "a" logo and the code PK. KALETRA is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules in the following package sizes:

Bottles of 180 capsules each…… (**NDC** 0074-3959-77)

Recommended storage: Store KALETRA soft gelatin capsules at 36 - 46°F (2 - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA capsules remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), capsules should be used within 2 months.

17 PATIENT COUNSELING INFORMATION

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

<u>Patients or parents of patients should be informed that:</u>

General Information

☐They should pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or underdose of KALETRA.

☐They should inform their healthcare provider if their children's weight changes in order to make sure that the child's KALETRA dose is the correct one.

☐They should take the prescribed dose of KALETRA as directed and to set up a daily routine in order to do so.

☐KALETRA capsules should be taken with food to enhance absorption.

☐Sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA 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 KALETRA 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 KALETRA and become harder to treat.

☐KALETRA 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 KALETRA.

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

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

Drug Interactions

☐KALETRA 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 KALETRA capsules.

☐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 KALETRA. The doctor may choose not to keep them on avanafil, or may adjust the dose of tadalafil while initiating treatment with KALETRA.

☐If they are receiving estrogen-based hormonal contraceptives, additional or alternate contraceptive measures should be used during therapy with KALETRA.

☐If they are taking or before they begin using Serevent® (salmeterol) and KALETRA, 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 KALETRA, 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 KALETRA or its components lopinavir and/or ritonavir. Patients should be advised to contact their healthcare provider if they develop a rash while taking KALETRA. 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 KALETRA. Pre-existing liver disease including Hepatitis B or C can worsen with use of KALETRA. 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 KALETRA 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 KALETRA 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 KALETRA as they may require a change in their diabetes treatment or new treatment.

☐KALETRA 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 KALETRA and a PDE 5 Inhibitor such as Viagra, Cialis or Levitra.

☐Redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

☐Patients should be informed that there may be a greater chance of developing diarrhea with the once daily regimen as compared with the twice daily regimen.

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MEDICATION GUIDE

KALETRA® (kuh-LEE-tra)

(lopinavir/ritonavir)

Capsules

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

What is the most important information I should know about KALETRA?

KALETRA may cause serious side effects, including:

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

Tell your doctor right away if you have any of these symptoms while taking KALETRA:

- dizziness
- lightheadedness
- fainting
- sensation of abnormal heartbeats

See "What are the possible side effects of KALETRA?" for more information about serious side effects.

What is KALETRA?

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

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

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

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

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

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

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

Who should not take KALETRA?

Do not take KALETRA if you take any of the following medicines:

- alfuzosin (Uroxatral®)
- cisapride (Propulsid®, Quicksolv®)
- colchicine (Colcrys®), if you have kidney and/or liver problems
- dronedarone (Multaq®)
- elbasvir/grazoprevir (Zepatier®)
- 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
- lurasidone (Latuda®), 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 can happen if you or your child take any of the medicines listed above with KALETRA.

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

What should I tell my doctor before taking KALETRA?

KALETRA may not be right for you. Tell your doctor about all your medical conditions, including if you:

- have any heart problems, including if you have a condition called Congenital Long QT Syndrome.
- have or had pancreas problems.
- have liver problems, including Hepatitis B or Hepatitis C.
- have diabetes.
- have hemophilia. People who take KALETRA may have increased bleeding.
- have low potassium in your blood.
- are pregnant or plan to become pregnant. It is not known if KALETRA will harm your unborn baby. **Pregnancy Registry.** There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of the pregnancy registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- **Do not breastfeed.** We do not know if KALETRA can be passed to the baby through your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

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

Especially tell your doctor if you take:

- medicine to treat HIV
- estrogen-based contraceptives (birth control pills and patches). KALETRA may reduce the effectiveness of estrogen-based contraceptives. During treatment with KALETRA, you should use a different type or an extra form of birth control. Talk to your doctor about what types of birth control you can use to prevent pregnancy while taking KALETRA.
- medicines to prevent organ transplant rejection
- medicines to treat cancer
- amiodarone (Cordarone®, Pacerone®)
- atorvastatin (Lipitor®)
- atovaquone (Marlarone®, Mepron®)
- avanafil (Stendra®), sildenafil (Viagra®), tadalafil (Cialis®), or vardenafil (Levitra®) for the treatment of erectile dysfunction (ED). If you get dizzy or faint (low blood pressure), have vision changes or have an erection that last longer than 4 hours, call your doctor or get medical help right away
- bedaquiline (Sirturo®)
- 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®)
- felodipine
- fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Subsys®)
- fluticasone (Cutivate®, Flonase®, Flovent®, Flovent Diskus®, Flovent HFA®, Veramyst®)
- isavuconazonium (Cresemba®)
- itraconazole (Onmel®, Sporanox®)
- ketoconazole (Extina®, Ketozole®, Nizoral®, Xolegel®)
- lamotrigine (Lamictal®)
- lidocaine
- methadone hydrochloride (Dolphine hydrochloride, Methadose®)
- nicardipine (Cardene®)
- nifedipine (Adalat CC®, Afeditab CR®, Procardia®)
- ombitasvir/parataprevir/ritonavir and dasabuvir (Viekira Pak®)
- 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®)
- simeprevir (Olysio®)
- tadalafil (Adcirca®) for the treatment of pulmonary arterial hypertension
- trazodone (Oleptro®)
- valproate (Depakote®, Depakene®, Depacon®)
- voriconazole (Vfend®)
- warfarin (Coumadin®, Jantoven®)

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

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

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

How should I take KALETRA?

- Take KALETRA every day exactly as prescribed by your doctor.
- It is very important to set up a dosing schedule and follow it every day.
- Do not change your treatment or stop treatment without first talking with your doctor.
- KALETRA capsules must be taken with food.
- If you are taking both didanosine (Videx®) and KALETRA:

- Didanosine should be taken one hour before or two hours after KALETRA.

- Do not miss a dose of KALETRA. This could make the virus harder to treat. If you forget to take KALETRA, take the missed dose right away. If it is almost time for your next dose, do not take the missed dose. Instead, follow your regular dosing schedule by taking your next dose at its regular time. Do not take more than one dose of KALETRA at one time.
- If you take more than the prescribed dose of KALETRA, call your doctor or go to the nearest emergency room right away.
- If your child is prescribed KALETRA, tell your doctor if your child's weight changes.
- KALETRA **should not** be given one time each day in children. When giving KALETRA to your child, give KALETRA exactly as prescribed.
- When your KALETRA supply starts to run low, get more from your doctor or pharmacy. It is important not to run out of KALETRA. The amount of HIV-1 virus in your blood may increase if the medicine is stopped for even a short time. The virus may become resistant to KALETRA and become harder to treat.

What are the possible side effects of KALETRA?

KALETRA can cause serious side effects including:

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

- **Changes in body fat**. Changes in body fat in some people who take antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.
- **Increased bleeding for hemophiliacs**. Some people with hemophilia have increased bleeding with protease inhibitors including KALETRA.
- **Allergic reactions.** Skin rashes, some of them severe, can occur in people who take KALETRA. Tell your healthcare provider if you had a rash when you took another medicine for your HIV-1 infection or if you notice any skin rash when you take KALETRA.

- Common side effects of KALETRA include:
  - diarrhea
  - nausea
  - increased fats in blood (triglycerides or cholesterol)
  - vomiting

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

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

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

How should I store KALETRA?

- Store KALETRA in a refrigerator, between 36°F to 46°F (2°C to 8°C). KALETRA that is kept refrigerated may be used until the expiration date printed on the label.
- KALETRA that is stored at room temperature less than 77°F (25°C) should be used within 2 months.
- Keep KALETRA away from heat.
- Throw away any medicine that is out of date or that you no longer need.

Keep KALETRA and all medicines out of the reach of children.

General information about KALETRA

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

This Medication Guide summarizes the most important information about KALETRA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about KALETRA that is written for health professionals. For more information about KALETRA call 1-800-633-9110 or go to www.KALETRA.com.

What are the ingredients in KALETRA?

Active ingredients: lopinavir and ritonavir

Inactive ingredients:

FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

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

AbbVie Inc.,

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