PRESCRIBING INFORMATION

Name of the medicinal product:

KALETRA 200 MG/50 MG Tablets, Film Coated for Oral use

Qualitative and quantitative composition:

KALETRA 200 MG/50 MG Tablets:

Each film-coated tablet contains 200 mg of lopinavir co-formulated with 50 mg of ritonavir as a pharmacokinetic enhancer.

For the full list of excipients, see section 10.

1 INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Limitations of Use:

- Genotypic or phenotypic testing and/or treatment history should guide the use of KALETRA . The number of baseline lopinavir resistance-associated substitutions affects the virologic response to KALETRA *[see Microbiology (11.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Administration Recommendations

KALETRA tablets may be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

2.2 Dosage Recommendations in Adults

KALETRA can be given in once daily or twice daily dosing regimen at dosages noted in Tables 1 and 2.
KALETRA once daily dosing regimen is not recommended in:

- Adult patients with three or more of the following lopinavir resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V *[see Microbiology (11.4)].*
- In combination with carbamazepine, phenobarbital, or phenytoin *[see Drug Interactions (7.3)].*
- In combination with efavirenz, nevirapine, or nelfinavir *[see Drug Interactions (7.3) and Clinical Pharmacology 11.3)].*
- In pregnant women *[see Dosage and Administration (.23), Use in Specific Populations (8.1) and Clinical Pharmacology (11.3)].*

Table 1. Recommended Dosage in Adults- KALETRA Once Daily Regimen

KALETRA Dosage Form	Recommended Dosage
200 mg/50 mg Tablets	800 mg/200 mg (4 tablets) once daily

Table 2. Recommended Dosage in Adults- KALETRA Twice Daily Regimen

KALETRA Dosage Form	Recommended Dosage
200 mg/50 mg Tablets	400 mg/100 mg (2 tablets) twice daily

The dose of KALETRA must be increased when administered in combination with efavirenz, nevirapine or nelfinavir. Table 3 outlines the dosage recommendations for twice daily dosing when KALETRA is taken in combination with these agents.

Table 3. Recommended Dosage in Adults- KALETRA Twice Daily Regimen in Combination with Efavirenz, Nevirapine, or Nelfinavir

KALETRA Dosage Form	Recommended Dosage
200 mg/50 mg Tablets and 100 mg/25 mg Tablets	500 mg/125 mg (2 tablets of 200 mg/50 mg + 1 tablet of 100 mg/25 mg) twice daily

2.3 Dosage Recommendations in Pregnancy

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

- Once daily KALETRA dosing is not recommended in pregnancy *[see Use in Specific Populations (8.1) and Clinical Pharmacology (11.3)].*
- There are insufficient data to recommend dosing in pregnant women with any documented lopinavir-associated resistance substitutions.
- No dosage adjustment of KALETRA is required for patients during the postpartum period.

3 DOSAGE FORMS AND STRENGTHS

- **KALETRA 200 MG/50 MG Tablets***, 200 mg lopinavir, 50 mg ritonavir:* Red, film-coated, ovaloid, debossed with the “a” logo and the code AL containing 200 mg lopinavir and 50 mg ritonavir.

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 [see Drug Interactions (7.3) and Clinical Pharmacology (11.3)].
  - Alpha 1- Adrenoreceptor Antagonist : alfuzosin

- Antianginal: ranolazine
- Antiarrhythmic: dronedarone
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide
- Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine
- GI Motility Agent: cisapride
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- HMG-CoA Reductase Inhibitors: lovastatin, simvastatin
- Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide
- PDE5 Inhibitor: sildenafil when used for the treatment of pulmonary arterial hypertension
- Sedative/Hypnotics: triazolam, orally administered midazolam

- 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 [see Drug Interactions (7.3) and Clinical Pharmacology (11.3)].
  - Anticancer Agents: apalutamide
  - Antimycobacterial: rifampin
  - Herbal Products: St. John's Wort (hypericum perforatum)

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of 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 7 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)].* Consider the potential for drug interactions prior to and during 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 (8.5)]*.

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 (11.3)]*.

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 Clinical Pharmacology (11.3)]*.

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, autoimmune hepatitis, 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) and Drug Interactions (7.3)]*

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 cross-resistance among protease inhibitors has not been fully explored in KALETRA-treated patients, it is unknown what effect therapy with KALETRA will have on the activity of subsequently administered protease inhibitors. *[see Microbiology (11.4)].*

5.12 Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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 Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

Adverse Reactions in Adults

The safety of 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 4):

Table 4. 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 5 (treatment-naïve patients) and Table 6 (treatment-experienced patients).

Table 5. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

		Study 863 (48 Weeks)		**Study 720 (360 Weeks)**	**Study 730 (48 Weeks)**	
Variable	**Limit[1]**	**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 Once Daily + TDF +FTC (N=333)**	**KALETRA Twice Daily + TDF +FTC (N=331)**
Chemistry	**High**					
Glucose	> 250 mg/dL	2%	2%	4%	0%	<1%
Uric Acid	> 12 mg/dL	2%	2%	5%	<1%	1%
SGOT/ AST[2]	> 180 U/L	2%	4%	10%	1%	2%
SGPT/	>215 U/L	4%	4%	11%	1%	1%

ALT[2]						
GGT	>300 U/L	N/A	N/A	10%	N/A	N/A
Total Cholesterol	>300 mg/dL	9%	5%	27%	4%	3%
Triglycerides	>750 mg/dL	9%	1%	29%	3%	6%
Amylase	>2 x ULN	3%	2%	4%	N/A	N/A
Lipase	>2 x ULN	N/A	N/A	N/A	3%	5%
Chemistry	**Low**					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	2%	2%
Hematology	**Low**					
Neutrophils	<0.75 x 10^9/L	1%	3%	5%	2%	1%

1 ULN = upper limit of the normal range; N/A = Not Applicable.

2 Criterion for Study 730 was >5x ULN (AST/ALT).

Table 6. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

		Study 888 (48 Weeks)		**Study 957[2] and Study 765[3] (84-144 Weeks)**	**Study 802 (48 Weeks)**	
Variable	**Limit[1]**	**KALETRA 400/100 mg Twice Daily + NVP + NRTIs (N = 148)**	**Investigator-Selected Protease Inhibitor(s) + NVP + NRTIs (N = 140)**	**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)**
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).

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 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].*

Renal and Urinary Disorders
Nephrolithiasis

Skin and Appendages

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

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 7.
Additionally, KALETRA induces glucuronidation.
Published data suggest that lopinavir is an inhibitor of OATP1B1.
These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with lopinavir/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

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 7 provides a listing of established or potentially clinically significant drug interactions. Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction *[see Contraindications (4), Warnings and Precautions (5.1), Clinical Pharmacology (11.3)]* for magnitude of interaction.

Table 7. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Lopinavir or Concomitant Drug**	**Clinical Comments**
HIV-1 Antiviral Agents		
HIV-1 Protease Inhibitor: fosamprenavir/ritonavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse reactions has been observed with co-administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: indinavir*	↑ indinavir	Decrease indinavir dose to 600 mg twice daily, when co-administered with 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	KALETRA once daily in combination with nelfinavir is not recommended *[see Dosage and Administration (2)].*
HIV-1 Protease Inhibitor:	↑ lopinavir	Appropriate doses of additional

ritonavir*		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, 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 tablets to 500/125 mg when KALETRA tablet is co-administered with efavirenz or nevirapine. KALETRA once daily in combination with efavirenz or nevirapine is not recommended *[see Dosage and Administration (2)]*.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		KALETRA tablets can be administered simultaneously with didanosine without 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		
Alpha 1- Adrenoreceptor Antagonist: alfuzosin	↑ alfuzosin	Contraindicated due to potential hypotension [see Contraindications (4)].
Antianginal: ranolazine	↑ ranolazine	Contraindicated due to potential for serious and/or life-threatening reactions [see Contraindications (4)].
Antiarrhythmics: dronedarone	↑ dronedarone	Contraindicated due to potential for cardiac arrhythmias [see Contraindications (4)].
Antiarrhythmics e.g . amiodarone, bepridil, lidocaine (systemic), quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with KALETRA.
Anticancer Agents: abemaciclib apalutamide encorafenib ibrutinib ivosidenib dasatinib, neratinib, nilotinib, venetoclax,	↑ anticancer agents ↓lopinavir/ritonavir#	Apalutamide is contraindicated due to potential for loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors *[see Contraindications (4)].* Avoid co-administration of encorafenib or ivosidenib with KALETRA due to potential risk of

vinblastine vincristine		serious adverse events such as QT interval prolongation. If co-administration of encorafenib with KALETRA cannot be avoided, modify dose as recommended in encorafenib Prescribing Information. If co-administration of ivosidenib with KALETRA cannot be avoided, reduce ivosidenib dose to 250 mg once daily. Avoid use of neratinib, venetoclax or ibrutinib with KALETRA. 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 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*, itraconazole, voriconazole isavuconazonium sulfate*	↑ ketoconazole ↑ itraconazole ↓ voriconazole ↑ isavuconazonium	High doses of ketoconazole (>200 mg/day) or 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	Contraindicated due to potential for serious and/or life-threatening reactions 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: rifampin	↓ lopinavir	Contraindicated due to potential loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents *[see Contraindications (4)]*.
Antimycobacterial: bedaquiline	↑ bedaquiline	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/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: lurasidone	↑ lurasidone	Contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
pimozide	↑ pimozide	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics: quetiapine	↑ quetiapine	<u>Initiation of KALETRA in patients taking quetiapine:</u> Consider alternative antiretroviral therapy to avoid increases in

		quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. Initiation of quetiapine in patients taking KALETRA: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
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.
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	Co-administration of bosentan in patients on KALETRA: 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. Co-administration of KALETRA in

		patients on bosentan: 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
Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine	↑ ergot derivatives	Contraindicated due to potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues *[see Contraindications (4)].*
GI Motility Agent: cisapride	↑ cisapride	Contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)].*
GnRH Receptor Antagonists: elagolix	↑ elagolix ↓ lopinavir/ritonavir	Concomitant use of elagolix 200 mg twice daily and KALETRA for more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and KALETRA to 6 months.
Hepatitis C direct acting antiviral: elbasvir/grazoprevir	↑ elbasvir/grazoprevir	Contraindicated due to increased risk of alanine transaminase (ALT) elevations *[see Contraindications (4)].*
Hepatitis C direct acting antivirals: boceprevir*	↓lopinavir ↓boceprevir ↓ ritonavir ↑ glecaprevir ↑ pibrentasvir	It is not recommended to co-administer KALETRA and boceprevir.,

glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir/voxilaprevir ombitasvir/paritaprevir/ritonavir and dasabuvir*	 ↑ simeprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir	glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir.
Herbal Products: St. John's Wort (hypericum perforatum)	↓ lopinavir	Contraindicated due to potential for loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors *[see Contraindications (4)]*.
Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide	 ↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ rosuvastatin ↑ lomitapide	Contraindicated due to potential for myopathy including rhabdomyolysis [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/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity *[see Contraindications (4)]*.
Immunosuppressants:	↑	Therapeutic concentration

e.g. cyclosporine, tacrolimus, sirolimus	immunosuppressants	monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Kinase Inhibitors: fostamatinib *(also see anticancer agents above)*	↑ fostamatinib metabolite R406	Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required.
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	Sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated due to the potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope [*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 with these drugs may result in an increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection. Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): Sildenafil is contraindicated *[see Contraindications (4)].* The following dose adjustments are recommended for use of tadalafil with KALETRA. <u>Co-administration of tadalafil in patients on KALETRA:</u> In patients receiving KALETRA for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability: <u>Co-administration of KALETRA in patients on tadalafil:</u>

		Avoid use of tadalafil during the initiation of KALETRA. Stop tadalafil at least 24 hours prior to starting KALETRA. After at least one week following the initiation of KALETRA, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE5 inhibitors for erectile dysfunction: It is recommended not to exceed the following doses: • Sildenafil: 25 mg every 48 hours • Tadalafil: 10 mg every 72 hours • Vardenafil: 2.5 mg every 72 hours Use with increased monitoring for adverse events.
Sedative/Hypnotics: triazolam, orally administered midazolam	↑ triazolam ↑ midazolam	Contraindicated due to potential for prolonged or increased sedation or respiratory depression [see Contraindications (4)].
Sedative/Hypnotics: parenterally administered midazolam	↑ midazolam	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.
Systemic/Inhaled/ Nasal/Ophthalmic Corticosteroids: e.g., betamethasone budesonide ciclesonide	↓ lopinavir ↑ glucocorticoids	Coadministration with oral dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to lopinavir. Consider alternative

dexamethasone fluticasone methylprednisolone mometasone prednisone triamcinolone		corticosteroids. Coadministration with corticosteroids whose exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone (whose PK and/or PD are less affected by strong CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.
* *see Clinical Pharmacology (*11.3*)* for magnitude of interaction. # refers to interaction with apalutamide.		

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

Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects compared to the background rate for major birth defects in the general population. No treatment-related malformations were observed when lopinavir in combination with ritonavir was

administered to pregnant rats or rabbits; however embryonic and fetal developmental toxicities occurred in rats administered maternally toxic doses.

Clinical Considerations

Dose Adjustments During Pregnancy and the Postpartum Period

Administer 400/100 mg of KALETRA twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions *[see Dosage and Administration (2.3) and Clinical Pharmacology (11.3)].* There are insufficient data to recommend KALETRA dosing for pregnant patients with any documented lopinavir-associated resistance substitutions. No dose adjustment of KALETRA is required for patients during the postpartum period.

Once daily KALETRA dosing is not recommended in pregnancy.

Data

Human Data

KALETRA was evaluated in 12 HIV-infected pregnant women in an open-label pharmacokinetic trial *[see Clinical Pharmacology (11.3)]*. No new trends in the safety profile were identified in pregnant women dosed with KALETRA compared to the safety described in non-pregnant adults, based on the review of these limited data.

Antiretroviral Pregnancy Registry Data: Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of over 3,000 exposures to lopinavir containing regimens (including over 1,000 exposed in the first trimester), there was no difference between lopinavir and overall birth defects compared with the rate for major birth defects in the general population. The prevalence of birth defects in live births was 2.1% (95% CI: 1.4%-3.0%) following first-trimester exposure to lopinavir-containing regimens and 3.0% (95% CI: 2.4%-3.8%) following second and third trimester exposure to lopinavir-containing regimens. Based on prospective reports from the APR of over 5,000 exposures to ritonavir containing regimens (including over 2,000 exposures in the first trimester) there was no difference between ritonavir and overall birth defects compared with the rate for major birth defects in the general population. The prevalence of birth defects in live births was 2.2% (95% CI: 1.7%-2.8%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%-3.6%) following second and third trimester exposure to ritonavir-containing regimens. For both lopinavir and ritonavir, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5 fold increase in risk of overall birth defects and a 2 fold increase in risk of birth defects in the cardiovascular and genitourinary systems.

Animal Data

Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats administered lopinavir in combination with ritonavir (on gestation days 6-17) at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7 times

(for lopinavir) and 1.8 times (for ritonavir) the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily). In a pre- and post-natal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21) occurred.
No embryonic and fetal developmental toxicities were observed in rabbits administered lopinavir in combination with ritonavir (on gestation days 6-18) at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6 times (for lopinavir) and similar to (for ritonavir) the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily).

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Because of the potential for: 1) HIV transmission (in HIV-negative infants), 2) developing viral resistance (in HIV- positive infants), and 3) adverse reactions in the breastfed infant, instruct mothers not to breastfeed if they are receiving KALETRA.

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 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.

8.5 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 (11.3)]*.

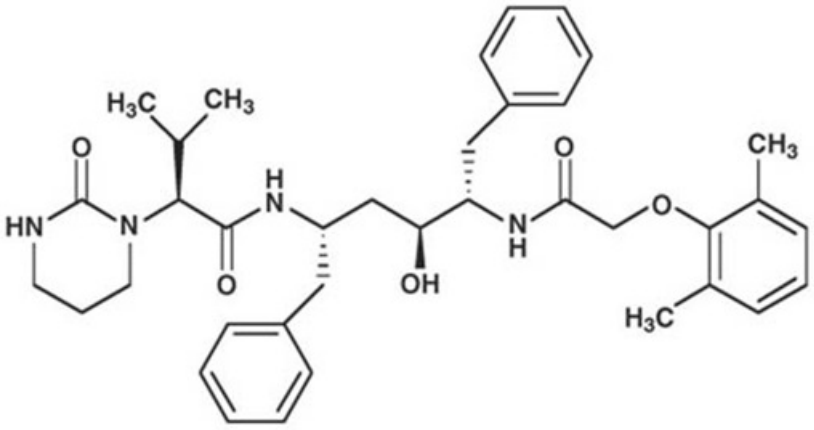
9 OVERDOSAGE

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 gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since lopinavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

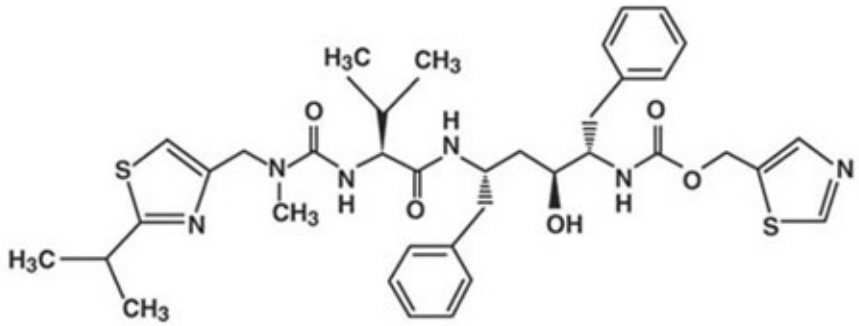
10 DESCRIPTION

KALETRA 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 tablets are available for oral administration in red tablets containing 200 mg of lopinavir and 50 mg of ritonavir, containing the following inactive ingredients:

Tablet contents: Copovidone K-value 28, Sorbitan laurate, Silica colloidal anhydrous, Sodium stearyl fumarate

Film-coating: Hypromellose 2910, Titanium dioxide, Macrogols type 400, Hydroxypropyl cellulose, Red ferric oxide E172, Talc, Macrogol type 3350, Silica colloidal anhydrous, Polysorbate 80.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

KALETRA is a fixed-dose combination of HIV-1 antiviral drugs lopinavir *[see Microbiology (11.4)]* and ritonavir. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

11.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of KALETRA on QTcF interval was evaluated in a placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 39 healthy adults. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction were 5.3 (8.1) and 15.2 (18.0) mseconds (msec) for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily KALETRA, respectively. KALETRA 800/200 mg twice daily resulted in a Day 3 mean Cmax approximately 2-fold higher than the mean Cmax observed with the approved once daily and twice daily KALETRA doses at steady state. The maximum mean (95% upper confidence bound) difference from placebo in the PR interval after baseline-correction were 24.9 (21.5, 28.3) and 31.9 (28.5, 35.3) msec for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily KALETRA, respectively *[see Warnings and Precautions (5.4, 5.5)]*.

11.3 Pharmacokinetics

The pharmacokinetic properties of lopinavir are summarized in Table 8. The steady-state pharmacokinetic parameters of lopinavir are summarized in Table 9. Under fed conditions, lopinavir concentrations were similar following administration of KALETRA tablets to capsules with less pharmacokinetic variability. Under fed conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA capsules and oral solution.

Table 8. Pharmacokinetic Properties of Lopinavir

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

Table 9. Steady-State Pharmacokinetic Parameters of Lopinavir, Mean ± SD

Pharmacokinetic Parameter	**Twice Daily**[a]	**Once Daily**[b]
C_{max} (µg/mL)	9.8 ± 3.7	11.8 ± 3.7
C_{min} (µg/mL)	5.5 ± 2.7	1.7 ± 1.6
AUC_{tau} (µg•h/mL)	92.6 ± 36.7	154.1 ± 61.4
a. 19 HIV-1 subjects, Kaletra 400/100 mg twice daily b. 24 HIV-1 subjects, Kaletra 800/200 mg + emtricitabine 200 mg + tenofovir DF 300 mg		

Specific Populations

Gender, Race and Age

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

Pregnancy

The C_{12h} values of lopinavir were lower during the second and third trimester by approximately 40% as compared to post-partum in 12 HIV-infected pregnant women received KALETRA 400 mg/100 mg twice daily. Yet this decrease is not considered clinically relevant in patients with no documented KALETRA-associated resistance substitutions receiving 400 mg/100 mg twice daily. *[see Use in Specific Populations (8.1)]*.

Renal Impairment

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

Hepatic Impairment

Multiple dosing of 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). KALETRA has not been studied in patients with severe hepatic impairment *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.5)]*.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*.

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.

The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in Table 10 (effect of other drugs on lopinavir) and Table 11 (effect of KALETRA on other drugs). For information regarding clinical recommendations, see Table 7 in *Drug Interactions (7)*.

Table 10. 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}
Efavirenz[1]	600 at bedtime	400/100 capsule twice daily	11, 7[3]	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 at bedtime	500/125 tablet twice daily	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 at bedtime	600/150 tablet twice daily	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Etravirine	200 twice daily	400/100 mg twice day (tablets)	16	0.89 (0.82-0.96)	0.87 (0.83-0.92)	0.80 (0.73-0.88)
Fosamprenavir[2]	700 twice daily plus ritonavir 100 twice daily	400/100 capsule twice daily	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole	200 single dose	400/100 capsule twice daily	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 twice daily	400/100 capsule twice daily	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 twice daily, steady-state	400/100 capsule twice daily	22, 19[3]	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg once daily; twice daily 1 wk	(> 1 yr) 300/75 mg/m^2 oral solution twice daily	12, 15[3]	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Ombitasvir/ paritaprevir/ ritonavir+dasabuvir[2]	25/150/100 + dasabuvir 400	400/100 tablet twice daily	6	0.87 (0.76, 0.99)	0.94 (0.81, 1.10)	1.15 (0.93, 1.42)
Omeprazole	40 once daily, 5 d	400/100 tablet twice daily, 10 d	12	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)

	40 once daily, 5 d	800/200 tablet once daily, 10 d	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
Pravastatin	20 once daily, 4 d	400/100 capsule twice daily, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Ranitidine	150 single dose	400/100 tablet twice daily, 10 d	12	0.99 (0.95, 1.03)	0.97 (0.93, 1.01)	0.90 (0.85, 0.95)
	150 single dose	800/200 tablet once daily, 10 d	10	0.97 (0.95, 1.00)	0.95 (0.91, 0.99)	0.82 (0.74, 0.91)
Rifabutin	150 once daily	400/100 capsule twice daily	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampin	600 once daily	400/100 capsule twice daily	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 once daily	800/200 capsule twice daily	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 once daily	400/400 capsule twice daily	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
Rilpivirine	150 once daily	400/100 twice daily (capsules)	15	0.96 (0.88-1.05)	0.99 (0.89-1.10)	0.89 (0.73-1.08)
Ritonavir	100 twice daily,	400/100 capsule twice daily	8, 21[3]	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tipranavir/ritonavir	500/200 twice daily	400/100 capsule twice daily	21 69[3]	0.53 (0.40, 0.69)	0.45 (0.32, 0.63)	0.30 (0.17, 0.51) 0.48[4] (0.40,

						0.58)

1 Reference for comparison is lopinavir/ritonavir 400/100 mg twice daily without efavirenz

2 Data extracted from the U.S. prescribing information of co-administered drugs.

3 Parallel group design

4 Drug levels obtained at 8-16 hours post-dose.

N/A = Not available.

Table 11. 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	N/A	N/A	1.22 (1.11, 1.34)	N/A
Efavirenz	600 at bedtime,	400/100 capsule twice daily	11, 12[3]	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Elbasvir/ grazoprevir[1]	50 once daily	400/100 twice daily	10	2.87 (2.29, 3.58)	3.71 (3.05, 4.53)	4.58 (3.72, 5.64)
	200 once daily		13	7.31 (5.65, 9.45)	12.86 (10.25, 16.13)	21.70 (12.99, 36.25)
Ethinyl Estradiol	35 µg once daily (Ortho Novum®)	400/100 capsule twice daily	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Etravirine	200 twice daily	400/100 tablet twice day	16	0.70 (0.64-0.78)	0.65 (0.59-0.71)	0.55 (0.49-0.62)
Fosamprenavir[1]	700 twice daily plus ritonavir 100 twice daily	400/100 capsule twice daily	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)

Indinavir	600 twice daily combo nonfasting vs. 800 three times daily alone fasting	400/100 capsule twice daily	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 capsule twice daily	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Maraviroc[1]	300 twice daily	400/100 twice daily	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)
Methadone	5 single dose	400/100 capsule twice daily	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nelfinavir	1000 twice daily combo vs. 1250 twice daily alone	400/100 capsule twice daily	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)
M8 metabolite				2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)
Nevirapine	200 once daily twice daily	400/100 capsule twice daily	5, 6[3]	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 once daily (Ortho Novum®)	400/100 capsule twice daily	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir[1]	25/150/100 + dasabuvir 400	400/100 tablet twice daily	6	1.14 (1.01, 1.28)	1.17 (1.07, 1.28)	1.24 (1.14, 1.34)
				2.04 (1.30, 3.20)	2.17 (1.63, 2.89)	2.36 (1.00, 5.55)
				1.55 (1.16, 2.09)	2.05 (1.49, 2.81)	5.25 (3.33, 8.28)
				0.99 (0.75,	0.93 (0.75,	0.68 (0.57,

				1.31)	1.15)	0.80)
Pitavastatin[1]	4 once daily	400/100 tablet twice daily	23	0.96 (0.84-1.10)	0.80 (0.73-0.87)	N/A
Pravastatin	20 once daily	400/100 capsule twice daily	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	150 once daily combo vs. 300 once daily alone	400/100 capsule twice daily	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-*O*-desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25-*O*-desacetyl rifabutin				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Rilpivirine	150 once daily	400/100 capsules twice daily	15	1.29 (1.18-1.40)	1.52 (1.36-1.70)	1.74 (1.46-2.08)
Rosuvastatin[2]	20 once daily	400/100 tablet twice daily	15	4.66 (3.4, 6.4)	2.08 (1.66, 2.6)	1.04 (0.9, 1.2)
Tenofovir alafenamide[1]	10 once daily	800/200 tablet once daily	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	N/A
Tenofovir disoproxil fumarate[1]	300 once daily	400/100 capsule twice daily	24	No Change	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

1 Data extracted from the U.S. prescribing information of co-administered drugs.

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

3 Parallel group design

N/A = Not available.

11.4 Microbiology

Mechanism of Action

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

Antiviral Activity

In the absence of human serum, the mean 50% effective concentration (EC_{50}) values of lopinavir against five different HIV-1 subtype B laboratory strains in lymphoblastic cell lines ranged from 10-27 nM (0.006-0.017 µg/mL, 1 µg/mL = 1.6 µM) and ranged from 4-11 nM (0.003-0.007 µg/mL) against several HIV-1 subtype B clinical isolates in peripheral blood lymphocytes (n = 6). In the presence of 50% human serum, the mean EC_{50} values of lopinavir against these five HIV-1 laboratory strains ranged from 65-289 nM (0.04-0.18 µg/mL), representing a 7- to 11-fold attenuation. The EC_{50} values of lopinavir against three different HIV-2 strains ranged from 12-180 nM (0.008-113 µg/mL).

Resistance

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

In a study of 653 antiretroviral treatment naïve patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV-1 RNA > 400 copies/mL at Week 24, 32, 40 and/or 48 were analyzed. No specific amino acid substitutions could be associated with resistance to KALETRA in the virus from 37 evaluable KALETRA-treated patients.

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 and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (> 400 copies/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. All four of these patients had previously received treatment with at least one protease inhibitor and had at least 4 substitutions associated with protease inhibitor resistance immediately prior to 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.

Cross-resistance - Nonclinical Studies

Varying degrees of cross-resistance have been observed among HIV-1 protease inhibitors. The antiviral activity in cell culture of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined (Table 12).

Table 12. Susceptibility Reduction to Lopinavir Against Isolates from Patients Previously Treated With a Single Protease Inhibitor

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

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

Clinical Studies - Antiviral Activity of 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 13 shows the 48-week virologic response (HIV-1 RNA <400 copies/mL) according to the number of the above protease inhibitor resistance-associated substitutions at baseline in studies 888 and 765 *[see Clinical Studies (13.2) and (13.3)]* 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 13. 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 >1,000 copies/mL despite previous therapy with at least two protease inhibitors selected from indinavir, nelfinavir, ritonavir, and saquinavir were randomized to receive one of two doses of 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 >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 14.

Table 14. 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.

12 NONCLINICAL TOXICOLOGY

12.1 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 $AUC_{0\text{-}24}$hr 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/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily).

13 CLINICAL STUDIES

13.1 Adult Patients without Prior Antiretroviral Therapy

Study 863: KALETRA Capsules twice daily + stavudine + lamivudine compared to nelfinavir three times daily + stavudine + lamivudine

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

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

Table 15. 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]	9%	25%

Rebound Never suppressed through Week 48	7% 2%	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 < 400 copies/mL (75% vs. 62%, respectively) and HIV-1 RNA < 50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV-1 RNA level subgroups is presented in Table 16.

Table 16. 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/mm^3 for the KALETRA arm and 195 cells/mm^3 for the nelfinavir arm.

Study 730: KALETRA Tablets once daily + tenofovir DF + emtricitabine compared to KALETRA Tablets twice daily + tenofovir DF + 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/mm^3 (range: 20 to 775 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL (range: 1.7 to 7.0 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 17.

Table 17. 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]	10%	8%
Rebound	5%	5%
Never suppressed through Week 48	5%	3%
Death	1%	<1%
Discontinued due to adverse events	4%	3%
Discontinued for other reasons[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 < 50 copies/mL (95% confidence interval for the difference, -5.9% to 6.8%). Mean $CD4^+$cell count increases at Week 48 were 186 cells/mm^3 for the KALETRA once-daily arm and 198 cells/mm^3 for the KALETRA twice daily arm.

13.2 Adult Patients with Prior Antiretroviral Therapy

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

Study 888 was a randomized, open-label, multicenter trial comparing treatment with 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/mm^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 $\log_{10}$ copies/mL (range: 2.6 to 6.0 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 18.

Table 18. 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]	24%	41%
Rebound	11%	19%
Never suppressed through Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons[3]	14%	13%

1 Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.

2 Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.

3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

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

Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 111 cells/mm^3 for the KALETRA arm and 112 cells/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/mm^3 (range: 4 to 952 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.3 log10 copies/mL (range: 1.7 to 6.6 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 19.

Table 19. 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/mm^3 for the once daily group and 122 cells/mm^3 for the twice daily group.

13.3 Other Studies Supporting Approval in Adult Patients

Study 720: KALETRA twice daily + stavudine + lamivudine

Study 765: KALETRA twice daily + nevirapine + NRTIs

Study 720 (patients without prior antiretroviral therapy) and study 765 (patients with prior protease inhibitor therapy) were randomized, blinded, multi-center trials evaluating treatment with 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/mm^3, respectively. Mean (range) baseline plasma HIV-1 RNA levels for patients in study 720 and study 765 were 4.9 (3.3 to 6.3) and 4.0 (2.9 to 5.8) $\log_{10}$ copies/mL, respectively.

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

Through 144 weeks of treatment in study 765, the proportion of patients with HIV-1 RNA < 400 (< 50) copies/mL was 54% (50%) [n = 70], and the corresponding mean increase in CD4$^+$cell count was 212

cells/mm^3. Twenty-seven patients (39%) discontinued the study, including 5 (7%) discontinuations secondary to adverse reactions and 2 (3%) deaths.

14 HOW SUPPLIED/STORAGE AND HANDLING

KALETRA® (lopinavir and ritonavir) 200 MG/50 MG tablets are red film-coated ovaloid tablets debossed with the "a" logo and the code AL.

Packages:

Bottles (HDPE) of 120 tablets

Blister PVC/Aluminium of 120 tablets

Not all pack sizes may be marketed.

Recommended Storage:

This medicine does not require any special storage conditions. But it is recommended to store at room temperature.

Dispense in original container.

15. MANUFACTURER:

AbbVie Deutschland GmbH & Co. KG., Knollstrasse, 67061 Ludwigshafen, Germany

16. LICENSE HOLDER:

AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel

17. REGISTRATION NUMBER:

Kaletra 200 mg/ 50 mg Tablets: 137-96-31542

Revised in October 2023 according to MOH guidelines.