PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**KALETRA®**

lopinavir/ritonavir

film-coated tablets (100/25 mg, 200/50 mg)

Pr**KALETRA®**

lopinavir/ritonavir

oral solution (80/20 mg/mL)

Human Immunodeficiency Virus (HIV) Protease Inhibitor (ATC Code: J05AR10)

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RECENT MAJOR LABEL CHANGES

2 Contraindications	07/2021
7 Warnings and Precautions	02/2020

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Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KALETRA (lopinavir/ritonavir) is indicated in combination with other antiretroviral agents when therapy is warranted for the treatment of HIV-1 infection.

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 **14 CLINICAL TRIAL** and **15 MICROBIOLOGY**)
- Genotypic or phenotypic testing and/or treatment history should guide the use of KALETRA. The number of baseline lopinavir-associated substitutions affects the virologic response of KALETRA (see **15 MICROBIOLOGY**).

1.1 Pediatrics

Pediatrics (6 months to 18 years of age): Based on a pediatric study, at week 24, the efficacy and safety with twice daily dosing in the pediatric population given KALETRA 100/25 mg tablets was consistent with the efficacy and safety findings in previous adult and pediatric studies using KALETRA twice daily (see Error! Reference source not found. **Study Results**).

The safety and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 6 months have not been established.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): 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.

2 CONTRAINDICATIONS

- KALETRA is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir. For a complete listing see the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A (cytochrome P450 3A) for clearance and for which elevated plasma levels may result in serious and/or life-threatening events. These drugs are listed in **Table *1*.**
- Co-administration of KALETRA is contraindicated with potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance. These drugs are listed in **Table *1***.
- KALETRA oral solution is contraindicated in pregnant women, patients with hepatic or renal failure and patients treated with disulfiram or metronidazole due to the potential risk of toxicity from the excipient propylene glycol (see **7 WARNINGS AND PRECAUTIONS** and **9 DRUG INTERACTIONS**).

Table 1 - Drugs that are Contraindicated with KALETRA

Drug Class	Drugs Within Class That Are Contraindicated with KALETRA	Clinical Comment
Alpha 1-adrenoreceptor antagonist	alfuzosin	Potential for serious reactions, such as hypotension.
Antianginal	ranolazine	Potential for serious and/or life-threatening reactions.
Antiarrhythmic	dronedarone	Potential for cardiac arrhythmias.
Antibiotic	fusidic acid	Potential of increased fusidic acid-associated adverse events, such as hepatitis or bone marrow suppression.
Anticancer	apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of KALETRA and potential loss of virologic response. In addition, exposure of apalutamide may increase with co-administration of KALETRA that may lead to increased adverse events including seizure and fracture.
	neratinib	Potential for serious and/or life-threatening reactions including hepatotoxicity.
	venetoclax[d]	Concomitant use of strong CYP3A inhibitors, such as KALETRA, and venetoclax may increase the risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase.
Antigout	colchicine, in patients with renal and/or hepatic impairment	Potential for serious and/or life-threatening reactions.
Antihistamines	astemizole[a], terfenadine[a]	Potential for serious and/or life-threatening reactions, such as cardiac arrhythmias.
Antimycobacterial	rifampin	Potential loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents. See (**9.4 Drug-Drug Interactions**) for further details.
Antipsychotics	lurasidone	Potential for serious and/or life-threatening reactions.
	pimozide	Potential for serious and/or life threatening reactions, such as cardiac arrhythmias.

Drug Class	Drugs Within Class That Are Contraindicated with KALETRA	Clinical Comment
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine[a], methylergonovine[a]	Potential for serious and/or life-threatening reactions, such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal (GI) Motility Agent	cisapride[a]	Potential for serious and/or life-threatening reactions, such as cardiac arrhythmias.
Herbal Products	St. John's Wort (*Hypericum perforatum*)	Potential loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors (see also **9.6 Drug-Herb Interactions**).
Hepatitis C Virus (HCV) Direct Acting Antiviral	elbasvir/grazoprevir	Potential for the increased risk of alanine transaminase (ALT) elevations.
Lipid-modifying agents HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for serious reactions, such as risk of myopathy including rhabdomyolysis (see also **7 WARNINGS AND PRECAUTIONS** and **Table 15**).
Microsomal triglyceride transfer protein (MTTP) Inhibitor	lomitapide	Potential for serious reactions, such as hepatotoxicity.
Long Acting Beta-Adrenoceptor Agonist	salmeterol	Potential for increased risk of cardiovascular adverse events associated with salmeterol.
PDE5 Inhibitors	sildenafil[b], only when used for the treatment of pulmonary arterial hypertension [PAH]	Potential increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection.
	vardenafil, when used for the treatment of erectile dysfunction or PAH	Potential increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection.
Sedatives/Hypnotics	orally administered midazolam[c], triazolam	Potential for serious and/or life-threatening reactions, such as prolonged or increased sedation or respiratory depression.

a. Product not marketed in Canada.
b. See **Table 15** for administration of sildenafil in patients with erectile dysfunction.
c. See **Table 15** for parenterally administered midazolam. Oral formulation of midazolam is not marketed in Canada.
d. See **Table 15** for coadministration of the maintenance dose of venetoclax.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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 should occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate (see **7 WARNINGS AND PRECAUTIONS**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

KALETRA must not be administered once daily in combination with efavirenz, nevirapine or nelfinavir (see **9 DRUG INTERACTIONS**).

KALETRA should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin. Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly. Co-administration of phenytoin and KALETRA resulted in moderate deceases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with KALETRA (see **9 DRUG INTERACTIONS**).

KALETRA must not be administered once daily in pediatric patients.

KALETRA once daily is not recommended in pregnant women (see **4.2 Recommended Dose and Dosage Adjustment**).

The once daily administration of KALETRA is not recommended for adult patients with 3 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 **15 MICROBIOLOGY**).

Concomitant therapy of efavirenz, nevirapine or nelfinavir may affect the dose of KALETRA (see **4.2 Recommended Dose and Dosage Adjustment, Adult Patients, *Concomitant Therapy*** and **4.2 Recommended Dose and Dosage Adjustment**, **Pediatric Patients, *Concomitant Therapy: Efavirenz, Nevirapine or Nelfinavir***).

KALETRA tablets may be taken with or without food.

KALETRA oral solution must be taken with food.

KALETRA tablets should be swallowed whole and not chewed, broken, or crushed.

4.2 Recommended Dose and Dosage Adjustment

The recommended oral dose of KALETRA is as follows (please also refer to **1 INDICATIONS**):

Adult Patients

Twice Daily Administration

- KALETRA tablets 400/100 mg (given as two 200/50 mg tablets) twice daily.
- KALETRA oral solution 400/100 mg (given as 5.0 mL of 80/20 mg/mL oral solution) twice daily.

- KALETRA should be given as twice-daily dosing regimen in patients with 3 or more resistance-associated substitutions.

Once Daily Administration

- KALETRA tablets 800/200 mg (given as four 200/50 mg tablets) once daily in patients with less than 3 protease-inhibitor associated mutations.
- KALETRA oral solution 800/200 mg (given as 10.0 mL) once daily in patients with less than 3 protease-inhibitor associated mutations.

KALETRA once-daily is not recommended in patients with 3 or more lopinavir resistance-associated mutations, in patients taking efavirenz, nevirapine or nelfinavir, and in pregnant women (see **4.1** Error! Reference source not found.).

Concomitant Therapy

Efavirenz, Nevirapine, or Nelfinavir:

- A dose increase of KALETRA tablets to 500/125 mg twice daily (given as two 200/50 mg tablets and one 100/25 mg tablet) should be considered when used in combination with efavirenz, nevirapine, or nelfinavir in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **9 DRUG INTERACTIONS**).
- A dose increase of KALETRA oral solution to 533/133 mg (given as 6.5 mL oral solution) twice daily may be considered when used in combination with efavirenz, nevirapine, or nelfinavir in the treatment of experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **9 DRUG INTERACTIONS**).

Pediatrics (6 months to 18 years)

KALETRA tablets and oral solution should not be administered once daily in pediatric patients less than 18 years of age.

Total amounts of alcohol and propylene glycol from all medicines, including KALETRA oral solution, that are to be given to infants should be taken into account in order to avoid toxicity from these excipients. KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities (see **7 WARNINGS AND PRECAUTIONS** and **7.1.3 Pediatrics** and **5 OVERDOSAGE**).

In children 6 months to 18 years of age, the recommended dosage of KALETRA should be calculated based on body weight (kg) or body surface area (BSA – m^2) and should not exceed the recommended adult dose.

Body surface area (BSA) can be calculated with the following equation:

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

The KALETRA dose can be calculated based on weight or BSA as follows:

Based on Weight	Patient's weight (kg) x Prescribed lopinavir dose (mg/kg) = administered lopinavir dose (mg)
Based on BSA	Patient's BSA (m^2) x Prescribed lopinavir dose (mg/m^2) = administered lopinavir dose (mg)

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

Volume of KALETRA oral solution (mL) = administered lopinavir dose (mg) ÷ 80 (mg/mL).

The dose of the oral solution should be administered using a calibrated oral dosing syringe.

Before prescribing KALETRA 100/25 mg tablets, children should be assessed for the ability to swallow intact tablets. If a child is unable to reliably swallow a KALETRA tablet, the KALETRA oral solution formulation should be prescribed.

Health care professionals should pay special attention to the accurate calculation of the dose of KALETRA, transcription of the medication orders, dispensing information and dosing instructions to minimize the risk for medication errors, overdose (see **5 OVERDOSAGE**) and underdose. Prescribers should calculate the appropriate dose based on body weight or body surface area (BSA) recommendations outlined in **Table 2**, **Table 3**, **Table 4**, **Table 5**, **Table 6**, and **Table 7** for each individual child and depending on concomitant therapy.

Without Concomitant Efavirenz, Nevirapine or Nelfinavir

Dosing Recommendations Using Tablets

Table 2 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on weight or BSA for KALETRA 100/25 mg tablets.

Table 2 - Pediatric Dosing Guidelines Based on Weight or BSA for KALETRA 100/25 mg Tablets – Without Concomitant Efavirenz, Nevirapine or Nelfinavir

Weight (kg)	Body Surface Area (m^2)[a]	Number of 100/25 mg Tablets Twice Daily[b]
7 to < 15 kg	0.4 to < 0.6	Tablets are not recommended. Use oral solution.
15 to 25 kg	≥ 0.6 to < 0.9	2 tablets (200/50 mg)
> 25 to 35 kg	≥ 0.9 to < 1.4	3 tablets (300/75 mg)
> 35 kg	≥ 1.4	4 tablets (400/100 mg) (or two 200/50 mg tablets)

a. Body surface area can be calculated with the equation presented in **4.2 Recommended Dose and Dosage Adjustment**.
b. KALETRA tablets may be taken with or without food.

Dosing Recommendations Using Oral Solution

Table 3 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on weight for KALETRA oral solution.

Table 3 - Pediatric Dosing Guidelines Based on Weight for KALETRA Oral Solution – Without Concomitant Efavirenz, Nevirapine or Nelfinavir

Weight (kg)	Twice Daily Dose (mg/kg)[a]	Volume of Oral Solution Twice Daily (80 mg lopinavir/20 mg ritonavir per mL)[b]
7 to < 15 kg	**12 mg/kg**	
7 to 10 kg		1.25 mL
> 10 to < 15 kg		1.75 mL
15 to 40 kg	**10 mg/kg**	
15 to 20 kg		2.25 mL
> 20 to 25 kg		2.75 mL
> 25 to 30 kg		3.50 mL
> 30 to 35 kg		4.00 mL
> 35 to 40 kg		4.75 mL
> 40 kg	See adult dosage recommendation	

a. Dosing based on the lopinavir component of KALETRA oral solution (80 mg/20 mg per mL).
b. KALETRA oral solution should be taken with food.

Table 4 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on body surface area for KALETRA oral solution.

Table 4 - Pediatric Dosing Guidelines Based on BSA for KALETRA Oral Solution – Without Concomitant Efavirenz, Nevirapine or Nelfinavir

Body Surface Area (m^2)[a]	Volume of Oral Solution Twice Daily (80 mg lopinavir/20 mg ritonavir per mL)[b] (230/57.5 mg/m^2)
0.25	0.7 mL (57.5/14.4 mg)
0.5	1.4 mL (115/28.8 mg)
0.75	2.2 mL (172.5/43.1 mg)
1.0	2.9 mL (230/57.5 mg)
1.25	3.6 mL (287.5/71.9 mg)
1.5	4.3 mL (345/86.3 mg)
1.75	5 mL (400/100 mg)

a. Body surface area can be calculated with the equation presented **4.2 Recommended Dose and Dosage Adjustment**.
b. KALETRA oral solution should be taken with food.

Concomitant Therapy: Efavirenz, Nevirapine or Nelfinavir

A dose increase of KALETRA, should be considered when used in combination with efavirenz, nevirapine, or nelfinavir in the treatment of experienced children 6 months to 18 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **9 DRUG INTERACTIONS**). Refer to **Table 5**, **Table 6** and **Table 7**.

Dosing Recommendations Using Tablets

Table 5 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on weight or body surface area for KALETRA 100/25 mg tablets.

Table 5 - Pediatric Dosing Guidelines Based on Weight or BSA for KALETRA 100/25 mg Tablets – With Concomitant Efavirenz, Nevirapine or Nelfinavir

Body Weight (kg)	Body Surface Area (m^2)[a]	Recommended Number of 100/25 mg Tablets Twice Daily[b]
7 to < 15	0.4 to < 0.6	Tablets are not recommended. Use oral solution.
15 to 20	≥ 0.6 to < 0.8	2 tablets (200/50 mg)
> 20 to 30	≥ 0.8 to < 1.2	3 tablets (300/75 mg)
> 30 to 45	≥ 1.2 to < 1.4	4 tablets (400/100 mg) (or two 200/50 mg tablets)
> 45	≥ 1.4	5 tablets (500/125 mg) (or two 200/50 mg tablets and one 100/25 mg tablets)

a. Body surface area can be calculated with the equation presented in **4.2 Recommended Dose and Dosage Adjustment**.
b. KALETRA tablets may be taken with or without food.

Dosing Recommendations Using Oral Solution

Table 6 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on weight for KALETRA oral solution.

Table 6 - Pediatric Dosing Guidelines Based on Weight for KALETRA Oral Solution – with Concomitant Efavirenz, Nevirapine or Nelfinavir

Weight (kg)	Twice Daily Dose (mg/kg)[a]	Volume of Oral Solution Twice Daily (80 mg lopinavir/20 mg ritonavir per mL)[b]
7 to < 15 kg	**13 mg/kg**	
7 to 10 kg		1.50 mL
> 10 to < 15 kg		2.00 mL
15 to 45 kg	**11 mg/kg**	
15 to 20 kg		2.50 mL
> 20 to 25 kg		3.25 mL
> 25 to 30 kg		4.00 mL
> 30 to 35 kg		4.50 mL
> 35 to 45 kg		5.00 mL
> 45 kg		6.50 mL

a. Dosing based on the lopinavir component of KALETRA oral solution (80 mg/20 mg per mL).
b. KALETRA oral solution should be taken with food.

Table 7 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on body surface area for KALETRA oral solution.

Table 7 - Pediatric Dosing Guidelines Based on BSA for KALETRA Oral Solution – With Concomitant Efavirenz, Nevirapine or Nelfinavir

Body Surface Area (m^2)[a]	Twice Daily Dose (300/75 mg/m^2)[b]
0.25	0.9 mL (75/18.8 mg)
0.5	1.9 mL (150/37.5 mg)
0.75	2.8 mL (225/56.3 mg)
1.0	3.8 mL (300/75 mg)
1.25	4.7 mL (375/93.8 mg)
1.5	5.6 mL (450/112.5 mg)
1.75	6.5 mL (525/131.3 mg)

a. Body surface area can be calculated with the equation presented in **4.2 Recommended Dose and Dosage Adjustment**.
b. KALETRA oral solution should be taken with food.

Pregnant Women

Administer 400 mg/100 mg of KALETRA twice daily in pregnant patients with no documented lopinavir-associated resistance-substitutions. There are insufficient data to recommend KALETRA dosing for pregnant patients with any documented lopinavir associated substitutions.

Once daily KALETRA dosing is not recommended in pregnancy.

No dosage adjustment of KALETRA is required for patients during postpartum period.

Avoid use of KALETRA oral solution during pregnancy due to the alcohol content. KALETRA oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v).

4.3 Reconstitution

Not applicable.

4.4 Administration

Not applicable.

4.5 Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

5 OVERDOSAGE

Overdoses with KALETRA oral solution have been reported. One of these reports described fatal cardiogenic shock in a 2.1 kg infant who received a single dose of 6.5 mL of KALETRA oral solution 9 days prior. However, a causal relationship between the overdose and the outcome could not be established. The following events have been reported in association with unintended overdoses in preterm neonates: complete AV block, cardiomyopathy, lactic acidosis, and acute renal failure.

Healthcare professionals should be aware that KALETRA oral solution is highly concentrated and contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v), and therefore, should pay special attention to accurate calculation of the dose of KALETRA, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors and overdose. This is especially important for infants and young children (see **1 INDICATIONS**, **4 DOSAGE AND ADMINISTRATION** and **7.1.3 Pediatrics**).

Accidental ingestion of KALETRA oral solution by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol (see **7.1.3 Pediatrics** and **4.2 Recommended Dose and Dosage Adjustment**).

- There is no specific antidote for overdose with KALETRA.
- 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.
- Administration of activated charcoal should be used to aid in removal of unabsorbed drug.
- Human experience of acute overdosage with KALETRA is limited.
- Since KALETRA is highly protein bound, dialysis is unlikely to be beneficial. However, dialysis can remove both alcohol and propylene glycol in the case of overdose with KALETRA oral solution.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 8 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	film-coated tablets (lopinavir/ritonavir)/ 100/25 mg, 200/50 mg	Each 100/25 mg tablet contains: copovidone, colloidal silicon dioxide, sodium stearyl fumarate and sorbitan monolaurate. The film-coating ingredients include: polyethylene glycol 3350, polyvinyl alcohol, talc, titanium dioxide, and yellow ferric oxide E172. Each 200/50 mg tablet contains: copovidone, colloidal silicon dioxide, sodium stearyl fumarate and sorbitan monolaurate. The film-coating ingredients include: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc, titanium dioxide, and yellow ferric oxide E172.
	oral solution (lopinavir/ritonavir)/ 80/20 mg/mL	Each mL of oral solution contains 80 mg of lopinavir and 20 mg of ritonavir with the following non-medicinal ingredients: acesulfame potassium, alcohol, artificial cotton

		candy flavour, citric acid, glycerine, high fructose corn syrup, Magnasweet 110 flavour, menthol, natural and artificial vanilla flavour, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water. The oral solution contains about 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v).

KALETRA (lopinavir/ritonavir) Film-Coated Tablets

KALETRA tablets are available in 2 strengths: 100 mg lopinavir/25 mg ritonavir and 200 mg lopinavir/50 mg ritonavir.

KALETRA 100 mg lopinavir/25 mg ritonavir tablets are supplied as pale yellow film-coated tablets debossed with the Abbott logo and the Abbo-Code KC. Each bottle contains 60 tablets.

KALETRA 200 mg lopinavir/50 mg ritonavir tablets are supplied as yellow film-coated tablets debossed with the Abbott logo and the Abbo-Code KA. Each bottle contains 120 tablets.

KALETRA (lopinavir/ritonavir) Oral Solution

KALETRA oral solution is a light yellow to orange-coloured liquid supplied in amber-coloured multiple-dose bottles. Each multi-dose bottle contains 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL) packaged with a marked dosing cup in the following size: 160 mL bottle.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

Drug-Drug Interactions

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 the area under the plasma concentration-time curve (AUC) (> 3-fold) when co-administered with KALETRA. Additionally, KALETRA induces glucuronidation which may affect the exposure of certain drugs.

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.

KALETRA should not be used in combination with quetiapine. Monitoring and dose reduction may be required if necessary (see **Table 15**).

Steps describing the prevention or management of these possible and known drug interactions, including dosing recommendations, are provided in **Table 15**. Consider the potential for drug interaction prior to and during KALETRA therapy, review concomitant medications during KALETRA therapy, and monitor for the adverse reactions associated with the concomitant medications (see **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS**).

Carcinogenesis and Mutagenesis

For a brief discussion of pre-clinical animal data, see **16 NON-CLINICAL TOXICOLOGY**.

Cardiovascular

PR Interval Prolongation

In a Phase 1 study in healthy volunteers, mean change from baseline in PR interval of 11.6 to 31.2 msec was noted in subjects receiving KALETRA on Study Day 3 when exposures were up to 3-fold higher than observed with recommended once daily or twice daily KALETRA doses at steady state. Maximum PR interval was 286 msec and no second- or third-degree heart block was observed.

There have been post-marketing reports of asymptomatic prolongation of the PR interval in some patients receiving combination antiretroviral therapy containing lopinavir/ritonavir. Reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil, calcium blockers, beta-adrenergic blockers, digoxin and atazanavir) have been reported in patients receiving KALETRA. KALETRA should be used with caution in such patients, particularly with those drugs metabolized by CYP3A (see **10.2 Pharmacodynamics**).

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 QT interval (see **10 CLINICAL PHARMACOLOGY**).

Endocrine and Metabolism

Diabetes Mellitus/Hyperglycemia

Levels of blood glucose may increase during antiretroviral therapy. Such changes may in part be linked to the treatment per se [e.g., protease inhibitors (PIs)], and in part to disease control and lifestyle. 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 PI 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 PI 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 PI therapy and these events has not been established. For monitoring of blood glucose, reference is made to established HIV treatment guidelines. Glucose elevations should be managed as clinically appropriate (see **7 WARNINGS AND PRECAUTIONS**).

Lipid Elevations

Levels of blood lipids may increase during antiretroviral therapy. Such changes may in part be linked to the treatment per se (e.g., protease inhibitors), and in part to disease control and lifestyle (see **Table 13** and **Table 14**).

Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy (see **7 WARNINGS AND PRECAUTIONS**). For monitoring of blood lipids, reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate, taking into consideration any potential drug-drug interactions with KALETRA and HMG-CoA reductase inhibitors (see **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS**).

Hematologic

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors (PIs). In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced. A causal relationship between PI therapy and these events has not been established; however, the frequency of bleeding episodes should be closely monitored in patients on KALETRA.

Hepatic/Biliary/Pancreatic

Hepatic

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment. KALETRA has not been studied in patients with severe hepatic impairment. Pharmacokinetic data suggests increases in lopinavir plasma concentrations of approximately 30% as well as decreases in plasma protein binding in HIV and hepatitis C virus (HCV) co-infected patients with mild to moderate hepatic impairment (see **10.2 Pharmacokinetics**). Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing or worsening of transaminases elevations or hepatic decompensation with use of KALETRA.

There have been post-marketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV 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.

Increased aspartate transaminase (AST) and alanine transaminase (ALT) monitoring should be considered in these patients, especially during the first several months of KALETRA treatment (see **7 WARNINGS AND PRECAUTIONS**).

Pancreatic

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 elevation is a risk factor for

development of pancreatitis (see **7 WARNINGS AND PRECAUTIONS**). Patients with advanced HIV 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.

Immune

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including KALETRA. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections [such as Mycobacterium avium-complex (MAC), cytomegalovirus (CMV), Pneumocystis jirovecii pneumonia (PCP), and tuberculosis (TB)], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) 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.

Monitoring and Laboratory Tests

Appropriate laboratory testing of liver enzymes should be conducted prior to initiating therapy with KALETRA and close monitoring should be performed during treatment. Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. For monitoring of liver enzymes, blood lipids, and glucose refer to established HIV treatment guidelines.

Sensitivity/Resistance

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of KALETRA therapy on the efficacy of subsequently-administered PIs is under investigation. HIV-1 isolates with reduced susceptibility to lopinavir have been selected in vitro. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses in vitro. The selection of resistance to KALETRA therapy in antiretroviral treatment-naïve patients has not yet been characterized in vivo (see **15 MICROBIOLOGY**).

Sensitivity

The presence of high level alcohol in KALETRA oral solution is potentially harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease, as well as for pregnant women and children. It may modify or increase the effects of the other medicines (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**).

Patients taking KALETRA oral solution, particularly those with renal impairment or with decreased ability to metabolize propylene glycol (e.g., those of Asian origin), should be monitored for adverse reactions potentially related to propylene glycol toxicity (i.e., seizures, stupor, tachycardia, hyperosmolarity, lactic acidosis, renal toxicity, haemolysis).

KALETRA oral solution contains up to 0.8 g of fructose per dose when taken according to the dosage recommendations. This may be unsuitable in hereditary fructose intolerance.

KALETRA oral solution contains up to 0.3 g of glycerol per dose. Only at high inadvertent doses, it can cause headache and gastrointestinal upset. Furthermore, polyoxol 40 hydrogenated castor oil and potassium present in KALETRA oral solution may cause only at high inadvertent doses gastrointestinal upset. Patients on a low potassium diet should be cautioned.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women.

Based on limited pharmacokinetics data from a published literature, 12 HIV-infected pregnant women received KALETRA 400 mg/100 mg (two 200/50 mg tablets) twice daily as part of an antiretroviral regimen. Plasma concentrations of lopinavir were measured over 12-hour periods during the second trimester (20 to 24 weeks gestation), the third trimester (30 weeks gestation) and at 8 weeks post-partum. The C_{12h} values of lopinavir were lower during the second and third trimester by approximately 40% as compared to post-partum.

No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities occurred in rats at a maternally toxic dose (see **16 NON-CLINICAL TOXICOLOGY**).

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).

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.

In post-marketing surveillance through the Antiretroviral Pregnancy Registry, established since January 1989, based on prospective reports of over 3000 exposures to lopinavir containing regimens (including over 1000 exposed in the first trimester), there was no difference between lopinavir and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the

Metropolitan Atlanta Congenital Defects Program (MACDP). Based on prospective reports from the APR of over 5000 exposures to ritonavir containing regimens (including over 2000 exposures in the first trimester) there was no difference between ritonavir and overall birth defects compared with the U.S. background rate (MACDP). For both lopinavir and ritonavir, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. The prevalence of birth defects after any trimester exposure to KALETRA is comparable to the prevalence observed in the general population. The population exposed and monitored to date is only sufficient to detect major teratogenicity, and cannot detect an increase in the risk of relatively rare defects, however no pattern of birth defects suggestive of a common etiology was seen.

7.1.2 Breast-feeding

HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. 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 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving KALETRA**.

7.1.3 Pediatrics

Pediatrics (6 months to 18 years of age): KALETRA should not be administered once daily to pediatric patients less than 18 years of age (see **4 DOSAGE AND ADMINISTRATION** and **10 CLINICAL PHARMACOLOGY**).

Toxicity in Preterm Neonates

A safe and effective dose of KALETRA oral solution in the preterm neonate population has not been established. KALETRA oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities (see **5 OVERDOSAGE**). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations.

Preterm neonates may be at an increased risk of propylene glycol associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients. Infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to lopinavir/ritonavir oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis.

Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving KALETRA oral solution.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): For a brief discussion, see **1 INDICATIONS**.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adult Patients

The safety of KALETRA has been investigated in 2,612 patients in Phase 2 to 4 clinical trials, of which more than 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.

Commonly reported adverse reactions to KALETRA during clinical trials 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.

Cumulative treatment-emergent adverse reactions of moderate or severe intensity are identified in **Table 11**.

Pediatric Patients

KALETRA has been studied in 273 pediatric patients 6 months to 18 years of age. The adverse event profile seen during clinical trials was similar to that for adult patients (see **14.2 Study Results**).

Dysgeusia (22%), vomiting (21%), and diarrhea (12%) were the most common adverse reactions of any severity and of probable, possible or unknown relationship to KALETRA oral solution in pediatric patients treated with combination therapy for up to 48 weeks in Study M98-940. A total of 8 subjects experienced adverse events of moderate to severe intensity and of possible, probable, or unknown relationship to KALETRA, which include: allergic reaction (characterized by fever, rash, and jaundice), fever, viral infection, constipation, hepatomegaly, pancreatitis, vomiting, serum glutamic pyruvic transaminase (SGPT) increased, dry skin, rash, and dysgeusia. Rash was the only event of those listed that occurred in 2 or more subjects (n=3).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adult Patients

Drug-related clinical adverse events of moderate or severe intensity in ≥ 2% of patients treated with combination therapy including KALETRA for up to 48 weeks (Phase 3) and for up to 360 weeks (Phase 1/2) are presented in **Table 9**. For other information regarding observed or potentially serious adverse events, see **7 WARNINGS AND PRECAUTIONS**.

Percentages of patients with selected treatment-emergent adverse events of moderate or severe intensity reported in ≥ 2% of adult PI-experienced patients are listed in **Table 10**. The incidence of diarrhea during 48 weeks of therapy was similar for KALETRA tablets dosed once daily compared to KALETRA tablets dosed twice daily in Study M05-730.

Table 9 - Percentage of Patients with Selected Treatment-Emergent[a] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

	Study M98-863 (48 Weeks)		Study M02-418 (48 Weeks)		Study M97-720 (360 Weeks)	Study M05-730 (48 Weeks)	
	KALETRA capsules 400/100 mg b.i.d. + d4T + 3TC	nelfinavir 750 mg t.i.d. + d4T + 3TC	KALETRA capsules 800/200 mg daily + TDF + FTC	KALETRA capsules 400/100 mg b.i.d. + TDF + FTC	KALETRA capsules b.i.d.[b] + d4T + 3TC	KALETRA tablets[c] 800/200 mg daily + TDF + FTC	KALETRA tablets[c] 400/100 mg b.i.d. + TDF + FTC
	(N=326)	(N=327)	(N=115)	(N=75)	(N=100)	(N=333)	(N=331)
Endocrine Disorders							
Hypogonadism Male	0%	0%	0%	0%	2%	0%	0%
Gastrointestinal Disorders							
Diarrhea	16%	17%	16%	5%	28%	17%	15%
Nausea	7%	5%	9%	8%	16%	7%	5%
Vomiting	2%	2%	3%	4%	6%	3%	4%
Abdominal Pain	4%	3%	3%	3%	11%	1%	1%
Dyspepsia	2%	< 1%	0%	1%	6%	0%	0%
Flatulence	2%	1%	2%	1%	4%	1%	1%
Abdominal Distension	< 1%	1%	1%	0%	4%	< 1%	< 1%
Abnormal Feces	0%	< 1%	0%	0%	8%	0%	0%
General Disorders and Administration Site Conditions							
Asthenia	4%	3%	0%	0%	9%	< 1%	< 1%
Pain	1%	0%	0%	0%	3%	0%	0%
Infections and Infestations							
Bronchitis	0%	0%	0%	0%	2%	0%	< 1%

	Study M98-863 (48 Weeks)		Study M02-418 (48 Weeks)		Study M97-720 (360 Weeks)	Study M05-730 (48 Weeks)	
	KALETRA capsules 400/100 mg b.i.d. + d4T + 3TC	nelfinavir 750 mg t.i.d. + d4T + 3TC	KALETRA capsules 800/200 mg daily + TDF + FTC	KALETRA capsules 400/100 mg b.i.d. + TDF + FTC	KALETRA capsules b.i.d.[b] + d4T + 3TC	KALETRA tablets[c] 800/200 mg daily + TDF + FTC	KALETRA tablets[c] 400/100 mg b.i.d. + TDF + FTC
	(N=326)	(N=327)	(N=115)	(N=75)	(N=100)	(N=333)	(N=331)
Investigations							
Weight decreased	1%	< 1%	0%	0%	2%	0%	< 1%
Metabolism and Nutrition Disorders							
Anorexia	1%	< 1%	1%	1%	2%	< 1%	1%
Musculoskeletal and Connective Tissue Disorders							
Myalgia	1%	1%	0%	0%	2%	0%	0%
Nervous System Disorders							
Headache	2%	2%	3%	3%	6%	2%	1%
Paresthesia	1%	1%	0%	0%	2%	0%	0%
Psychiatric Disorders							
Insomnia	2%	1%	0%	0%	3%	1%	0%
Depression	1%	2%	1%	0%	0%	0%	0%
Libido decreased	< 1%	< 1%	0%	1%	2%	0%	< 1%
Reproductive System and Breast Disorders							
Amenorrhea	0%	0%	5%	0%	0%	0%	0%
Skin and Subcutaneous Tissue Disorders							
Lipodystrophy Acquired	1%	1%	0%	0%	12%	0%	0%
Rash	1%	2%	1%	0%	5%	< 1%	1%
Vascular Disorders							
Vasodilatation	0%	0%	0%	0%	3%	0%	0%

	Study M98-863 (48 Weeks)		Study M02-418 (48 Weeks)		Study M97-720 (360 Weeks)	Study M05-730 (48 Weeks)	
	KALETRA capsules 400/100 mg b.i.d. + d4T + 3TC	nelfinavir 750 mg t.i.d. + d4T + 3TC	KALETRA capsules 800/200 mg daily + TDF + FTC	KALETRA capsules 400/100 mg b.i.d. + TDF + FTC	KALETRA capsules b.i.d.[b] + d4T + 3TC	KALETRA tablets[c] 800/200 mg daily + TDF + FTC	KALETRA tablets[c] 400/100 mg b.i.d. + TDF + FTC
	(N=326)	(N=327)	(N=115)	(N=75)	(N=100)	(N=333)	(N=331)

a. Includes adverse events of possible or probable relationship to study drug.

b. Includes adverse event data from dose group I (200/100 mg twice daily [N=16] and 400/100 mg twice daily only [N=16]) and dose group II (400/100 mg twice daily [N=35] and 400/200 mg twice daily [N=33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

c. In the first 8 weeks of the study, 166 and 165 of the patients received KALETRA capsule once daily and twice daily, respectively. After that period, all patients received KALETRA tablet.

Definitions: b.i.d. = twice daily; t.i.d. = three times daily; d4T = stavudine; 3TC = lamivudine; FTC = emtricitabine; TDF = tenofovir DF

Table 10 - Percentage of Patients with Selected Treatment-Emergent[a] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

	Study M98-888 (48 Weeks)		Study M98-957[b] and Study M97-765[c] (84 to 144 Weeks)	Study M06-802 (48 Weeks)	
	KALETRA capsules 400/100 mg b.i.d. + NVP + NRTIs	Investigator-selected PI(s) + NVP + NRTIs	KALETRA capsules b.i.d. + NNRTI + NRTIs	KALETRA tablets 800/200 mg daily + NRTIs	KALETRA tablets 400/100 mg b.i.d. + NRTIs
	(N=148)	(N=140)	(N=127)	(N=300)	(N=299)
Gastrointestinal Disorders					
Diarrhea	7%	9%	23%	14%	11%
Nausea	7%	16%	5%	3%	7%
Vomiting	4%	12%	2%	2%	3%
Abdominal Pain	2%	2%	4%	2%	< 1%

	Study M98-888 (48 Weeks)		Study M98-957[b] and Study M97-765[c] (84 to 144 Weeks)	Study M06-802 (48 Weeks)	
	KALETRA capsules 400/100 mg b.i.d. + NVP + NRTIs	Investigator-selected PI(s) + NVP + NRTIs	KALETRA capsules b.i.d. + NNRTI + NRTIs	KALETRA tablets 800/200 mg daily + NRTIs	KALETRA tablets 400/100 mg b.i.d. + NRTIs
	(N=148)	(N=140)	(N=127)	(N=300)	(N=299)
Abdominal Pain Upper	N/A	N/A	N/A	1%	2%
Flatulence	1%	2%	2%	1%	1%
Dysphagia	2%	1%	0%	0%	0%
Abnormal Feces	0%	0%	2%	0%	0%
General Disorders and Administration Site Conditions					
Asthenia	3%	6%	9%	< 1%	< 1%
Pyrexia	2%	1%	2%	0%	< 1%
Pain	0%	0%	4%	0%	0%
Chills	2%	0%	0%	0%	0%
Investigations					
Weight decreased	0%	1%	3%	< 1%	< 1%
Metabolism and Nutrition Disorders					
Anorexia	1%	3%	0%	0%	1%
Nervous System Disorders					
Headache	2%	3%	2%	< 1%	0%
Paresthesia	0%	1%	2%	0%	0%
Psychiatric Disorders					
Depression	1%	2%	3%	< 1%	0%
Insomnia	0%	2%	2%	0%	< 1%
Skin and Subcutaneous Tissue Disorders					
Lipodystrophy Acquired	1%	1%	6%	1%	1%

	Study M98-888 (48 Weeks)		Study M98-957[b] and Study M97-765[c] (84 to 144 Weeks)	Study M06-802 (48 Weeks)	
	KALETRA capsules 400/100 mg b.i.d. + NVP + NRTIs	Investigator-selected PI(s) + NVP + NRTIs	KALETRA capsules b.i.d. + NNRTI + NRTIs	KALETRA tablets 800/200 mg daily + NRTIs	KALETRA tablets 400/100 mg b.i.d. + NRTIs
	(N=148)	(N=140)	(N=127)	(N=300)	(N=299)
Rash	2%	1%	2%	0%	0%
Vascular Disorders					
Hypertension	0%	0%	2%	0%	0%

a. Includes adverse events of possible or probable relationship to study drug.

b. Includes adverse event 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.

c. Includes adverse event 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.

b, c: Average of Studies M98-957 and M97-765; both studies have subjects dosed with KALETRA + NNRTI + NRTIs.

Definitions: b.i.d. = twice daily; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; N/A = not applicable.

Cumulative Common Clinical Trial Adverse Reactions

The following have been identified as cumulative treatment-emergent adverse reactions of moderate to severe intensity (**Table 11**).

Table 11 - Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in ≥ 2% of Adult Patients Receiving KALETRA in Combined Phase 2 to 4 Studies (N=2,612)

System Organ Class / Adverse Drug Reactions*	n	%
Blood and Lymphatic System Disorders		
Anemia*	54	2.1
Gastrointestinal Disorders		
Abdominal pain (upper and lower) *	160	6.1
Diarrhea*	510	19.5
Dyspepsia	53	2.0
Gastroenteritis and colitis*	66	2.5
Nausea	269	10.3

System Organ Class / Adverse Drug Reactions*	n	%
Vomiting*	177	6.8
General Disorders and Administration Site Conditions		
Fatigue including asthenia*	198	7.6
Hepatobiliary Disorders		
Hepatitis including AST, ALT, and GGT increases*	91	3.5
Immune System Disorders		
Hypersensitivity including urticaria and angioedema*	70	2.7
Infections and Infestations		
Lower respiratory tract infection*	202	7.7
Skin infections including cellulitis, folliculitis, and furuncle*	86	3.3
Upper respiratory tract infection*	363	13.9
Metabolism and Nutrition Disorders		
Decreased appetite	52	2.0
Hypercholesterolemia*	192	7.4
Hypertriglyceridemia*	161	6.2
Weight decreased*	61	2.3
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain including arthralgia and back pain*	166	6.4
Nervous System Disorders		
Headache including migraine*	165	6.3
Insomnia*	99	3.8
Neuropathy and peripheral neuropathy*	51	2.0
Psychiatric Disorders		
Anxiety*	101	3.9
Skin and Subcutaneous Tissue Disorders		
Rash including maculopapular rash*	99	3.8
* Represents a medical concept including several similar MedDRA Preferred Terms (PTs)		

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3 to 4 laboratory abnormalities are presented in **Table 12**.

Table 12 - Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients

Variable	Limit	KALETRA oral solution b.i.d.[a] + NRTIs (N=100)
Chemistry	**High**	
Sodium	> 149 mmol/L	3%
Total Bilirubin	> 2.9 x ULN	4%
SGOT/AST	> 180 U/L	8%
SGPT/ALT	> 215 U/L	7%
Total Cholesterol	> 7.77 mmol/L	4%
Amylase	> 2.5 x ULN	6%
Chemistry	**Low**	
Sodium	< 130 mmol/L	3%
Calcium	< 1.75 mmol/dL	2%
Hematology	**Low**	
Hemoglobin	< 70 g/L	2%
Platelet Count	< 50 x 10^9/L	4%
Neutrophils	< 0.40 x 10^9/L	2%

a. Includes clinical laboratory data from the 230/57.5 mg/m^2 (n=49) and 300/75 mg/m^2 (n=51) dose arms.

Definitions: b.i.d. = twice daily; NRTI = nucleoside reverse transcriptase inhibitor; ULN = upper limit of the normal range; SGPT/ALT = serum glutamic-pyruvic transaminase/alanine aminotransferase; SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate aminotransferase.

8.3 Less Common Clinical Trial Adverse Reactions

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving KALETRA in all Phase 2 to 4 clinical trials and considered at least possibly related or of unknown relationship to treatment with KALETRA and of at least moderate intensity are listed below by system organ class.

Blood and Lymphatic System Disorders:	leukopenia and neutropenia*, lymphadenopathy*, splenomegaly
Cardiac Disorders:	angina pectoris, atherosclerosis, such as myocardial infarction*, atrial fibrillation, atrioventricular block*, palpitations, tricuspid valve incompetence*
Ear and Labyrinth Disorders:	hyperacusis, tinnitus, vertigo*

Endocrine Disorders:	Cushing's syndrome, hypogonadism*, hypothyroidism
Eye Disorders:	eye disorder, visual disturbance, visual impairment*
Gastrointestinal Disorders:	abdominal discomfort, abdominal distension, constipation*, dry mouth, duodenitis and gastritis*, enteritis, enterocolitis, enterocolitis hemorrhagic, eructation, esophagitis, fecal incontinence, flatulence, gastroesophageal reflux disease (GERD)*, gastric disorder, gastric ulcer, gastrointestinal hemorrhage including rectal hemorrhage*, hemorrhoids, gastrointestinal ulcer*, pancreatitis*, periodontitis, rectal hemorrhage, stomach discomfort, stomatitis and oral ulcers*
General Disorders and Administration Site Conditions:	chest pain, cyst, drug interaction, edema, edema peripheral, face edema, hypertrophy, malaise
Hepatobiliary Disorders:	cholangitis, cholecystitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, jaundice, liver tenderness
Immune System Disorders:	drug hypersensitivity, immune reconstitution inflammatory syndrome.
Infection and Infestations:	bacterial infection, bronchopneumonia, influenza, otitis media, perineal abscess, pharyngitis, rhinitis, sialoadenitis, sinusitis, viral infections
Investigations:	drug level increased, glucose tolerance decreased
Metabolism and Nutrition Disorders:	blood glucose disorders including diabetes mellitus*, dehydration, dyslipidaemia, hypovitaminosis, increased appetite, lactic acidosis*, lipomatosis, obesity, weight increased*
Musculoskeletal and Connective Tissue Disorders:	arthropathy, muscle disorders, such as weakness and spasms*, myalgia*, osteoarthritis, osteonecrosis, pain in extremity, rhabdomyolysis*
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps):	benign neoplasm of skin, lipoma, neoplasm
Nervous System Disorders:	ageusia*, amnesia, ataxia, balance disorder, cerebral infarction, cerebral vascular event*, convulsion*, dizziness*, dysgeusia, dyskinesia, encephalopathy, extrapyramidal disorder, facial palsy, hypertonia, somnolence, tremor*
Psychiatric Disorders:	abnormal dreams*, affect lability, agitation, apathy, confusional state, disorientation, libido decreased, mood swings, nervousness, thinking abnormal
Renal and Urinary Disorders:	hematuria*, nephritis*, nephrolithiasis, renal disorder, renal failure*, urine abnormality, and urine odor abnormal

Reproductive System and Breast Disorders:	breast enlargement, menstrual disorders including amenorrhea, menorrhagia*, ejaculation disorder, erectile dysfunction*, gynecomastia
Respiratory, Thoracic and Mediastinal Disorders:	asthma, cough, dyspnea, pulmonary edema
Skin and Subcutaneous Tissue Disorders:	acne, alopecia, capillaritis and vasculitis*, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, dermatitis/rash including eczema and seborrheic dermatitis*, dry skin, hyperhidrosis, idiopathic capillaritis, nail disorder, night sweats*, pruritus*, rash generalized, seborrhea, skin discoloration, skin hypertrophy, skin striae, skin ulcer, swelling face
Vascular Disorders:	deep vein thrombophlebitis, deep vein thrombosis*, orthostatic hypertension*, hypotension, thrombophlebitis, varicose vein, vasculitis
*Represents a medical concept including several similar MedDRA Preferred Terms (PTs)	

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

The percentages of adult antiretroviral-naïve and PI-experienced patients treated with combination therapy including KALETRA with Grade 3 to 4 laboratory abnormalities are presented in **Table 13** and **Table 14**.

Table 13 - Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

Variable	Limit	Study M98-888 (48 Weeks)		Study M02-418 (48 Weeks)		Study M97-720 (360 Weeks)	Study M05-730 (48 Weeks)	
		KALETRA capsules 400/100 mg b.i.d. + d4T + 3TC	Nelfinavir 750 mg t.i.d. + d4T + 3TC	KALETRA capsules 800/200 mg daily + TDF + FTC	KALETRA capsules 400/100 mg b.i.d. + TDF + FTC	KALETRA capsules b.i.d.[a] + d4T + 3TC	KALETRA tablets[b] 800/200 mg daily + TDF + FTC	KALETRA tablets[b] 400/100 mg b.i.d. + TDF + FTC
		(N=326)	(N=327)	(N=115)	(N=75)	(N=100)	(N=333)	(N=331)
Chemistry	**High**							
Glucose	> 13.8 mmol/L	2%	2%	3%	1%	4%	0%	< 1%
Uric Acid	> 0.71 mmol/L	2%	2%	0%	3%	5%	< 1%	1%

Variable	Limit	Study M98-888 (48 Weeks)		Study M02-418 (48 Weeks)		Study M97-720 (360 Weeks)	Study M05-730 (48 Weeks)	
		KALETRA capsules 400/100 mg b.i.d. + d4T + 3TC	Nelfinavir 750 mg t.i.d. + d4T + 3TC	KALETRA capsules 800/200 mg daily + TDF + FTC	KALETRA capsules 400/100 mg b.i.d. + TDF + FTC	KALETRA capsules b.i.d.[a] + d4T + 3TC	KALETRA tablets[b] 800/200 mg daily + TDF + FTC	KALETRA tablets[b] 400/100 mg b.i.d. + TDF + FTC
		(N=326)	(N=327)	(N=115)	(N=75)	(N=100)	(N=333)	(N=331)
SGOT/AST[c]	> 5 x ULN	2%	4%	5%	3%	10%	1%	2%
SGPT/ALT[c]	> 5 x ULN	4%	4%	4%	3%	11%	1%	1%
GGT	> 5 x ULN	N/A	N/A	N/A	N/A	10%	N/A	N/A
Total Cholesterol	> 7.77 mmol/L	9%	5%	3%	3%	27%	4%	3%
Triglycerides	> 8.25 mmol/L	9%	1%	5%	4%	29%	3%	6%
Amylase	> 2 x ULN	3%	2%	7%	5%	4%	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[d]	< 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%	1%	5%	2%	1%

Variable	Limit	Study M98-888 (48 Weeks)		Study M02-418 (48 Weeks)		Study M97-720 (360 Weeks)	Study M05-730 (48 Weeks)	
		KALETRA capsules 400/100 mg b.i.d. + d4T + 3TC	Nelfinavir 750 mg t.i.d. + d4T + 3TC	KALETRA capsules 800/200 mg daily + TDF + FTC	KALETRA capsules 400/100 mg b.i.d. + TDF + FTC	KALETRA capsules b.i.d.[a] + d4T + 3TC	KALETRA tablets[b] 800/200 mg daily + TDF + FTC	KALETRA tablets[b] 400/100 mg b.i.d. + TDF + FTC
		(N=326)	(N=327)	(N=115)	(N=75)	(N=100)	(N=333)	(N=331)

a. Includes adverse event data from dose group I (200/100 mg twice daily [N=16] and 400/100 mg twice daily only [N=16]) and dose group II (400/100 mg twice daily [N=35] and 400/200 mg twice daily [N=33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

b. In the first 8 weeks of the study, 166 and 165 of the patients received KALETRA capsule once daily and twice daily, respectively. After that period, all patients received KALETRA tablet.

c. Criterion for Study M05-730 was >5 x ULN (AST/ALT).

d. The Cockcroft-Gault formula was used to calculate creatinine clearance.

Definitions: b.i.d. = twice daily; t.i.d. = three times daily; d4T = stavudine; 3TC = lamivudine; FTC = emtricitabine; TDF = tenofovir DF; ULN = upper limit of the normal range; N/A = Not Applicable; SGPT/ALT = serum glutamic-pyruvic transaminase/alanine aminotransferase; SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase.

Table 14 - Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

Variable	Limit	Study M98-888 (48 Weeks)		Studies M98-957[a] and M97-765[b] (84 to 144 Weeks)	Study M06-802 (48 Weeks)	
		KALETRA capsules 400/100 mg b.i.d. + NVP + NRTIs	Investigator-selected PI(s) + NVP + NRTIs	KALETRA capsules b.i.d. + NNRTI + NRTIs	KALETRA tablets 800/200 mg daily + NRTIs	KALETRA tablets 400/100 mg b.i.d. + NRTIs
		(N=148)	(N=140)	(N=127)	(N=300)	(N=299)
Chemistry	**High**					
Glucose	> 13.8 mmol/L	1%	2%	5%	2%	2%

Variable	Limit	Study M98-888 (48 Weeks)		Studies M98-957[a] and M97-765[b] (84 to 144 Weeks)	Study M06-802 (48 Weeks)	
		KALETRA capsules 400/100 mg b.i.d. + NVP + NRTIs	Investigator-selected PI(s) + NVP + NRTIs	KALETRA capsules b.i.d. + NNRTI + NRTIs	KALETRA tablets 800/200 mg daily + NRTIs	KALETRA tablets 400/100 mg b.i.d. + NRTIs
		(N=148)	(N=140)	(N=127)	(N=300)	(N=299)
Total Bilirubin	> 59.5 mmol/L	1%	3%	1%	1%	1%
SGOT/AST[c]	> 5 x ULN	5%	11%	8%	3%	2%
SGPT/ALT[c]	> 5 x ULN	6%	13%	10%	2%	2%
GGT	> 5 x ULN	N/A	N/A	29%	N/A	N/A
Total Cholesterol	> 7.77 mmol/L	20%	21%	39%	6%	7%
Triglycerides	> 8.25 mmol/L	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%
Creatinine Phosphokinase	> 4 x ULN	N/A	N/A	N/A	4%	5%
Chemistry	**Low**					
Calculated Creatinine Clearance[d]	< 50 mL/min	N/A	N/A	N/A	3%	3%
Inorganic Phosphorous	< 0.48 mmol/L	1%	0%	2%	1%	<1%

Variable	Limit	Study M98-888 (48 Weeks)		Studies M98-957[a] and M97-765[b] (84 to 144 Weeks)	Study M06-802 (48 Weeks)	
		KALETRA capsules 400/100 mg b.i.d. + NVP + NRTIs	Investigator-selected PI(s) + NVP + NRTIs	KALETRA capsules b.i.d. + NNRTI + NRTIs	KALETRA tablets 800/200 mg daily + NRTIs	KALETRA tablets 400/100 mg b.i.d. + NRTIs
		(N=148)	(N=140)	(N=127)	(N=300)	(N=299)
Hematology	**Low**					
Neutrophils	0.75 x 10^9/L	1%	2%	4%	3%	4%
Hemoglobin	< 80 g/L	1%	1%	1%	1%	2%

a. Includes clinical laboratory data from patients receiving 400/100 mg capsules twice daily (n=29) or 533/133 mg capsules twice daily (n=28) for 84 weeks. Patients received KALETRA capsules in combination with NRTIs and efavirenz.

b. Includes clinical laboratory data from patients receiving 400/100 mg capsules twice daily (n=36) or 400/200 mg capsules twice daily (n=34) for 144 weeks. Patients received KALETRA capsules in combination with NRTIs and nevirapine.

c. Criterion for Study M06-802 was > 5 x ULN (AST/ALT).

d. The Cockcroft-Gault formula was used to calculate creatinine clearance.

Definitions: b.i.d. = twice daily; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; ULN = upper limit of the normal range; N/A = Not Applicable; SGPT/ALT = serum glutamic-pyruvic transaminase/alanine aminotransferase; SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase.

8.5 Post-Market Adverse Reactions

Hepatobiliary Disorders:	hepatitis
Metabolism and Nutrition Disorders:	new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia
	Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events
Skin and Subcutaneous Tissue Disorders:	toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme
Vascular Disorders:	bradyarrhythmia

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No drug interaction studies were performed with the once daily regimen of KALETRA .

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both in vitro and in vivo. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **Table 15**). 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.

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. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see **Table 15**). Co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations. These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with KALETRA. The healthcare provider should consult appropriate references for comprehensive information.

Published data suggest that KALETRA is an inhibitor of OATP1B1.

9.4 Drug-Drug Interactions

Possible Dose Adjustments Based on Drug-Drug Interactions

Table 15 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. The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir. See (**Table 16** and **Table 17**) for magnitude of interaction.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 15 - Established and Other Potentially Significant Drug Interactions with Lopinavir: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
HCV-Antiviral Agents		
HCV Protease Inhibitors: boceprevir[c]	↓ boceprevir ↓ lopinavir	Concomitant administration of boceprevir and KALETRA resulted in reduced boceprevir and lopinavir steady-state exposure. It is not recommended to co-administer KALETRA and boceprevir.
HCV Protease Inhibitors: glecaprevir/pibrentasvir	↑ glecaprevir	Concomitant administration of glecaprevir/pibrentasvir and lopinavir/ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
HCV Combination Drug: ombitasvir/paritaprevir/ ritonavir with or without dasabuvir[c]	↑ ombitasvir/ paritaprevir/ritonavir	Concentrations of ombitasvir, paritaprevir, and ritonavir may be increased when co-administered with KALETRA, therefore, co-administration is not recommended.
HCV Protease Inhibitors: simeprevir[c]	↑ simeprevir	Concomitant use of KALETRA and simeprevir may result in significantly increased plasma concentrations of simeprevir. It is not recommended to co-administer KALETRA and simeprevir.
HCV Combination Drug: sofosbuvir/velpatasvir/ voxilaprevir	↑ voxilaprevir	Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and lopinavir/ritonavir is not recommended due to the potential for increased toxicity, which may negatively affect compliance.
HCV Protease Inhibitors: telaprevir	↓ telaprevir ↔ lopinavir[b]	Concomitant administration of telaprevir and KALETRA resulted in reduced telaprevir steady-state exposure, while the lopinavir steady state exposure was not affected.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
HIV-Antiretroviral Agents		
HIV CCR5 – Antagonist maraviroc	↑ maraviroc lopinavir (not studied)	Concurrent administration of maraviroc with KALETRA will increase plasma levels of maraviroc. The dose of maraviroc should be decreased during co-administration with KALETRA 400/100 mg twice daily For further details, see complete prescribing information for maraviroc.
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz, nevirapine	↓ lopinavir ↔ efavirenz[b] ↔ nevirapine[b]	Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with KALETRA. KALETRA dose increase is recommended in all patients. A dose increase of KALETRA tablets to 500/125 mg twice daily (given as two 200/50 mg tablets and one 100/25 mg tablet) when used in combination with efavirenz resulted in similar lopinavir plasma concentrations compared to KALETRA tablets 400/100 mg twice daily without efavirenz (see **4 DOSAGE AND ADMINISTRATION**). A dose increase of KALETRA oral solution to 533/133 mg (6.5 mL) twice daily taken with food may be considered when used in combination with efavirenz or nevirapine in patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). KALETRA should not be administered once daily in combination with efavirenz or nevirapine (see **4 DOSAGE AND ADMINISTRATION**). Increasing the dose of KALETRA tablets to 600/150 mg (given as three 200/50 mg tablets) twice daily when co-administered with efavirenz significantly increased the

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
		lopinavir plasma concentrations approximately 35%, and ritonavir concentrations approximately 56 to 92%, compared to KALETRA tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz (see **9.2 Drug Interactions Overview**).
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine[c]	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Non-nucleoside Reverse Transcriptase Inhibitor: etravirine	↓ etravirine	Concomitant use of KALETRA with etravirine causes a decrease in the plasma concentrations of etravirine, but no dose adjustment is required. Refer to the etravirine Product Monograph for more information.
Non-nucleoside Reverse Transcriptase Inhibitor: rilpivirine	↑ rilpivirine	Concomitant use of KALETRA with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required. Refer to the rilpivirine Product Monograph for more information.
Nucleoside Reverse Transcriptase Inhibitor: didanosine	↔ didanosine	Dosage adjustment is not required. KALETRA tablets can be administered simultaneously with didanosine without food. For KALETRA oral solution, it is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given 1 hour before or 2 hours after KALETRA oral solution (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir	↑ tenofovir ↔ lopinavir[b]	KALETRA increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving KALETRA and tenofovir should be monitored for tenofovir-associated adverse events.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
Nucleoside Reverse Transcriptase Inhibitor: abacavir, zidovudine	↓ abacavir ↓ zidovudine	KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.
HIV Protease Inhibitor: fosamprenavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse events has been observed with the co-administration of KALETRA twice daily and fosamprenavir. The safety and efficacy of this combination have not been established.
fosamprenavir/ritonavir	↓ amprenavir ↑ lopinavir	The concomitant use of fosamprenavir/ritonavir and KALETRA is not recommended because of significant pharmacokinetic interactions (see **9.2 Drug Interactions Overview**).
HIV Protease Inhibitors: indinavir[c]	↑ indinavir ↔ lopinavir[b]	Decrease indinavir dose to 600 mg twice daily when co-administered with KALETRA 400/100 mg twice daily. KALETRA tablets once daily has not been studied in combination with indinavir.
HIV Protease Inhibitors: nelfinavir	↑ nelfinavir ↑ M8 metabolite of nelfinavir ↓ lopinavir	Nelfinavir induces the activity of CYP3A and thus has the potential to decrease plasma concentrations of other protease inhibitors when used in combination with KALETRA (see **4 DOSAGE AND ADMINISTRATION**). A dose increase of KALETRA to 533/133 mg (6.5 mL of oral solution) or 500/125 mg (given as two 200/50 mg tablets and one 100/25 mg tablet) twice daily may be considered in patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). The safety and efficacy of this combination have not been established. KALETRA should not be administered once daily in combination with nelfinavir.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
HIV Protease Inhibitors: ritonavir	↑ lopinavir	The safety and efficacy of this combination have not been established.
HIV Protease Inhibitors: saquinavir	↑ saquinavir ↔ lopinavir[b]	Saquinavir 1000 mg twice daily may be considered when co-administered with KALETRA 400/100 mg twice daily. KALETRA tablets once daily has not been studied in combination with saquinavir.
HIV Protease Inhibitors: tipranavir/ritonavir	↓ lopinavir	The concomitant administration of KALETRA and tipranavir co-administered with low-dose ritonavir is not recommended. Tipranavir (500 mg twice daily) with ritonavir (200 mg twice daily), co-administered with lopinavir/ritonavir (400/100 mg twice daily), resulted in a 55 and 70% reduction in lopinavir AUC and C_{min}, respectively.
Other Agents		
Analgesic: fentanyl	↑ fentanyl	The CYP3A inhibitor activity of KALETRA is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when KALETRA is co-administered with fentanyl, including extended-release, transdermal or transmucosal preparations.
Antialcoholics: disulfiram[c]/ metronidazole		KALETRA oral solution contains alcohol which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole). KALETRA oral solution is contraindicated in patients treated with disulfiram or metronidazole due to the potential risk of toxicity from the excipient propylene glycol (see **2 CONTRAINDICATIONS**).

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
Anticancer Agents: abemaciclib, apalutamide, dasatinib, encorafenib, ibrutinib, neratinib, nilotinib, vinblastine, vincristine	↑ anticancer agents	Potentially life-threatening adverse events associated with these anticancer agents have occurred as a result of having their serum concentrations increased when co-administered with KALETRA. Coadministration of apalutamide is contraindicated with KALETRA since apalutamide may decrease exposure of KALETRA with potential loss of virologic response. In addition, co-administration of apalutamide and KALETRA may lead to increased exposure of apalutamide resulting in increased potential for adverse events including seizure and fracture. Co-administration of KALETRA with ibrutinib is not recommended due to expected increase in ibrutinib exposure that could potentially result in a serious risk of tumor lysis syndrome. Coadministration of KALETRA with dasatinib should be avoided due to expected increase in dasatinib exposure. If the co-administration is unavoidable, close monitoring for toxicity and a dasatinib dose reduction should be considered (see SPRYCEL Product Monograph). Coadministration of encorafenib with KALETRA should be avoided due to potential increase in encorafenib exposure potentially increasing the risk of serious adverse events such as QT interval prolongation. If coadministration cannot be avoided, modify encorafenib dose as recommended in the encorafenib Product Monograph.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
		Coadministration of KALETRA with nilotinib should be avoided due to expected increase in nilotinib exposure. If the co-administration is unavoidable, close monitoring for the QT interval prolongation is recommended (see TASIGNA Product Monograph). Coadministration of KALETRA with abemaciclib should be avoided due to expected increase in abemaciclib exposure. If the co-administration is unavoidable, close monitoring for toxicity and an abemaciclib dose reduction should be considered (see VERZENIO Product Monograph). Coadministration of KALETRA with neratinib is contraindicated due to expected increase in neratinib exposure (see **2 CONTRAINDICATIONS**).
venetoclax	↑ venetoclax	Concomitant use of strong CYP3A inhibitors, such as KALETRA, and venetoclax may increase the risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase (see **2 CONTRAINDICATIONS**). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (see VENCLEXTA Product Monograph).
Anticoagulant: rivaroxaban	↑ rivaroxaban	Co-administration of rivaroxaban and KALETRA may result in significant changes in rivaroxaban exposures and may increase the risk of bleeding; therefore the combination should be avoided. For more detailed information please refer to the rivaroxaban Product Monograph.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
warfarin	↓ warfarin	Concentrations of warfarin may be affected. It is recommended that INR (International Normalized Ratio) be monitored.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ lopinavir ↓ phenytoin	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly. KALETRA should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin. In addition, co-administration of phenytoin and KALETRA resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with KALETRA.
lamotrigine, valproate	↓ lamotrigine ↓ valproate	Co-administration of KALETRA and either lamotrigine or valproate was associated with reduction in exposure of the anticonvulsant; 50% reduction in lamotrigine exposure has been reported. Use with caution. A dose increase of the anticonvulsant may be needed when coadministered with KALETRA and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments.
Antidepressants: bupropion	↓ bupropion ↓ hydroxybupropion ↔ lopinavir[b]	Concurrent administration of bupropion with KALETRA will decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion).
trazodone	↑ trazodone	Adverse events of nausea, dizziness, hypotension and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor, such as KALETRA, the combination should be used with caution and a lower dose of trazodone should be considered.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
Antigout Agents: colchicine	↑ colchicine	Concentrations of colchicine are expected to increase when co-administered with KALETRA. **For patients with renal and/or hepatic impairment:** Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir. For patients with renal and/or hepatic impairment co-administration of colchicine with KALETRA is contraindicated (see **2 CONTRAINDICATIONS**). **For patients with normal renal or hepatic function:** <u>Treatment of gout flares</u> 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. <u>Prophylaxis of gout flares</u> 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 daily).

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
Anti-infective: clarithromycin	↑ clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min, the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min, the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: itraconazole, ketoconazole	↑ itraconazole ↑ ketoconazole ↔ lopinavir[b]	High doses of ketoconazole or itraconazole (> 200 mg/day) are not recommended. Careful monitoring for adverse events and cautious use of ketoconazole or itraconazole is warranted at doses > 200 mg/day when administered with KALETRA. Administration of a single 200 mg dose of ketoconazole did not increase the C_{max}, AUC or C_{min} of lopinavir during KALETRA 400/100 mg twice daily administration. However, it is possible that with multiple administration or higher doses of ketoconazole, lopinavir concentrations could be moderately increased.
voriconazole	↓ voriconazole	A study has shown that co-administration of ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of lopinavir/ritonavir and voriconazole should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
Antimycobacterial: rifabutin	↑ rifabutin and rifabutin metabolite ↔ lopinavir[b]	Co-administration of KALETRA with rifabutin substantially increases concentration of rifabutin and its active metabolite by > 5-fold which may result in an increase in rifabutin-associated adverse events, including fever, neutropenia and uveitis. 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 events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
rifampin	↓ lopinavir	Large reductions in lopinavir plasma concentrations were observed in a study evaluating the combination of rifampin 600 mg once daily with KALETRA 400/100 mg twice daily. KALETRA should not be co-administered with rifampin as it may significantly decrease lopinavir's therapeutic effect. Results from studies using higher doses of KALETRA co-administered with rifampin indicated higher incidences of liver and gastrointestinal toxicity (see **2 CONTRAINDICATIONS**).
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however an increase in atovaquone doses may be needed.
Antipsychotics/Neuroleptics: lurasidone	↑ lurasidone	Due to CYP3A inhibition by KALETRA, concentrations of lurasidone are expected to increase. Co-administration of lurasidone with KALETRA is contraindicated (see **2 CONTRAINDICATIONS**).

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
pimozide	↑ pimozide	Co-administration of KALETRA with pimozide is contraindicated as it may lead to serious and/or life-threatening reactions, such as cardiac arrhythmias (see **2 CONTRAINDICATIONS**).
quetiapine	↑ quetiapine	Due to inhibition of CYP3A by KALETRA (lopinavir/ritonavir), co-administration of KALETRA with quetiapine may result in increased quetiapine concentrations. Serious and life-threatening quetiapine-related adverse reactions have been reported with CYP3A inhibitors. KALETRA should not be used in combination with quetiapine. Monitoring and dose reduction may be required if necessary.
Sedatives/Hypnotics: midazolam[c], oral	↑ midazolam	Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, KALETRA should not be given with orally administered midazolam (see **2 CONTRAINDICATIONS**).
midazolam, parental		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.
Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nicardipine[c], nifedipine	↑ dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
Cardiotonic Glycoside: digoxin	↑ digoxin	Co-administration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when co-administering KALETRA with digoxin, with appropriate monitoring of serum digoxin levels.
Corticosteroid: Systemic: dexamethasone	↓ lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Corticosteroid: Inhaled/Injectable/ Nasal: budesonide, fluticasone propionate, triamcinolone	↑ budesonide ↑ fluticasone ↑ triamcinolone	The concomitant use of KALETRA and inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone, or other glucocorticoids that are metabolized by CYP3A4 significantly increases the plasma concentration of fluticasone, budesonide, or triamcinolone, leading to significant decreases in the plasma concentration of cortisol. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during post-marketing administration of KALETRA with inhaled, injectable or intranasal fluticasone, budesonide, or triamcinolone. Co-administration of KALETRA and fluticasone, budesonide, or triamcinolone, therefore, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of glucocorticoid should be considered with close monitoring of local and systemic effects or consider alternatives (e.g. beclomethasone) to glucocorticoids which are not substrates of CYP3A4, particularly for long term use.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
Endothelin Receptor Antagonist: bosentan	↑ bosentan	Co-administration of bosentan and KALETRA increased steady state bosentan maximum concentrations (C_{max}) and AUC by 6-fold and 5-fold, respectively. <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.
GnRH Receptor Antagonists: elagolix	↑ elagolix	Coadministration of elagolix with KALETRA could increase elagolix exposure through inhibition of OATP, CYP3A, and P-gp. Known serious adverse events for elagolix include suicidal ideation and hepatic transaminase elevations. In addition, elagolix is a weak/moderate inducer of CYP3A, which may decrease exposure of KALETRA. Refer to the elagolix label for dosing information with strong CYP3A4 inhibitors.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
HMG-CoA Reductase Inhibitors: atorvastatin, rosuvastatin[d], pravastatin	↑ atorvastatin ↔ lopinavir[b] ↑ rosuvastatin ↔ lopinavir[b] ↑ pravastatin ↔ lopinavir[b]	HMG-CoA reductase inhibitors (statins) may interact with protease inhibitors and increase the risk of myopathy including rhabdomyolysis. The long-term safety when co-administering HMG-CoA reductase inhibitors with KALETRA has not been established. Concomitant use of protease inhibitors with lovastatin or simvastatin is contraindicated (see **2 CONTRAINDICATIONS**). Other HMG-CoA reductase inhibitors (statins) may also interact with protease inhibitors. This warning is based on clinical reports and on indirect evidence from studies on the cytochrome P450 CYP3A4 metabolism pathway. Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring. Consider other HMG-CoA reductase inhibitors, such as pravastatin or fluvastatin in combination with KALETRA. Note that an approximate 30% increase in pravastatin concentrations was observed and careful monitoring is warranted (see **9.2 Drug Interactions Overview**).
Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide	↑ lomitapide	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.
Immunosuppressants: cyclosporine, rapamycin[c], tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
Kinase Inhibitors (also see Anticancer agents above): fostamatinib	↑ fostamatinib	Coadministration of fostamatinib with KALETRA could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia. Monitor for toxicities of fostamatinib that may require fostamatinib dose modification (see fostamatinib Product Monograph).
Narcotic Analgesic: methadone	↓ methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.
Oral or Patch Contraceptive: ethinyl estradiol, norethindrone	↓ ethinyl estradiol ↓ norethindrone	Alternative or additional contraceptive measures should be used when estrogen-progesterone-based oral or patch contraceptives and KALETRA are co-administered.
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil lopinavir (not studied)	Particular caution should be used when prescribing PDE5 inhibitors for the treatment of erectile dysfunction in patients receiving KALETRA. Co-administration of KALETRA with these drugs is expected to substantially increase their concentrations and may result in increase in associated adverse events, such as hypotension, syncope, visual changes, and prolonged erection. <u>Use of PDE-5 Inhibitors for Erectile Dysfunction</u> Sildenafil may be used with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Tadalafil may be used with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Vardenafil should not be used with KALETRA (see **2 CONTRAINDICATIONS**).

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug[a]	Clinical Comments
		Use of PDE-5 Inhibitors for Pulmonary Arterial Hypertension Tadalafil may be used with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. When tadalafil is administered for the treatment of pulmonary arterial hypertension (PAH) to patients who are receiving KALETRA, refer to the tadalafil label for prescribing information. The use of sildenafil or vardenafil is contraindicated with KALETRA (see **2 CONTRAINDICATIONS**).

a. The magnitude (geometric mean ratio estimates) and direction (↑ increase; ↓ decrease; ↔ no effect) of the interaction are reported in **Table 16** and **Table 17**.
b. The "no effect" (↔) of geometric mean estimates are not considered clinically significant.
c. Product not marketed in Canada.

Drugs with No Observed or Predicted Interactions with KALETRA

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

Based on results of a desipramine interaction study, KALETRA does not inhibit CYP2D6-mediated metabolism at clinically relevant concentrations. However, caution should be used when co-administering either flecainide or propafenone with KALETRA.

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

Drug Interaction Studies

The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in **Table 16** (effect of other drugs on lopinavir) and **Table 17** (effect of KALETRA on other drugs).

Effect of Co-administered Drugs on Lopinavir

Table 16 - Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug (See Table 15 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg), Duration	Dose of KALETRA (mg), Duration	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Acid Reducing Agents						
Omeprazole	40 daily, 5 d	400/100 tablet b.i.d., 10 d	11	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)
		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)
Ranitidine	150 single dose	400/100 tablet b.i.d., 10 d	12	0.98 (0.95, 1.02)	0.98 (0.94, 1.01)	0.93 (0.89, 0.98)
		800/200 tablet once daily, 10 d	11	0.98 (0.95, 1.01)	0.96 (0.90, 1.02)	0.85 (0.67, 1.08)
Antifungal						
Ketoconazole	200 single dose	400/100 capsule b.i.d., 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Antimycobacterial						
Rifabutin	150 daily, 10 d	400/100 capsule b.i.d., 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)

Co-administered Drug	Dose of Co-administered Drug (mg), Duration	Dose of KALETRA (mg), Duration	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Rifampin	600 daily, 10 d	400/100 capsule b.i.d., 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 daily, 14 d[a]	800/200 capsule b.i.d., 9 d[b]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
		400/400 capsule b.i.d., 9 d[c]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
				Co-administration of KALETRA and rifampin is contraindicated (see **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS**).		
HCV-Antiviral Agents						
Boceprevir	800 mg q8h, 6 d	400/100 tablet b.i.d., 22 d	39	0.70 (0.65, 0.77)	0.66 (0.60, 0.72)	0.57 (0.49, 0.65)
Telaprevir	750 mg, q8h, 10 d	400/100 b.i.d., 20 d	12	0.96 (0.87, 1.05)	1.06 (0.96, 1.17)	1.14 (0.96, 1.36)
HIV-Antiretroviral Agents						
Efavirenz[d]	600 qHS, 9 d	400/100 capsule b.i.d., 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 qHS, 9 d	500/125 tablet b.i.d., 10 d	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)

Co-administered Drug	Dose of Co-administered Drug (mg), Duration	Dose of KALETRA (mg), Duration	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
	600 qHS, 9 d	600/150 tablet b.i.d., 10 d	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Fosamprenavir[e]	700 b.i.d. + ritonavir 100 b.i.d., 14 d	400/100 capsule b.i.d., 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Nelfinavir	1000 b.i.d., 10 d	400/100 capsule b.i.d., 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 b.i.d., steady-state (> 1 yr)[f]	400/100 capsule b.i.d., steady-state (> 1 yr)	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 daily, 2 wk, b.i.d. 1 wk[g]	300/75 mg/m^2 oral solution b.i.d., 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Ritonavir[d]	100 b.i.d., 3 to 4 wk[f]	400/100 capsule b.i.d., 3 to 4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir[h]	300 mg daily, 14 d	400/100 capsule b.i.d., 14 d	24	NC	NC	NC

Co-administered Drug	Dose of Co-administered Drug (mg), Duration	Dose of KALETRA (mg), Duration	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Tipranavir/ ritonavir[f]	500/200 mg b.i.d., (28 doses)	400/100 capsule b.i.d., (27 doses)	21 69	0.53 (0.40, 0.69)[i]	0.45 (0.32, 0.63)[i]	0.30 (0.17, 0.51)[i] 0.48 (0.40, 0.58)[j]
HMG-CoA Reductase Inhibitors						
Atorvastatin	20 daily, 4 d	400/100 capsule b.i.d., 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Pravastatin	20 daily, 4 d	400/100 capsule b.i.d., 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated. Drug interaction studies were not performed with the once daily regimen of KALETRA, except for omeprazole and ranitidine.

a. 28% ≥ Grade 2 transaminases were noted in this study.
b. 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.
c. 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.
d. The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.
e. Data extracted from the fosamprenavir labelling.
f. Study conducted in HIV-positive adult subjects.
g. Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.
h. Data extracted from the tenofovir labelling.
i. Intensive pharmacokinetic analysis.
j. Drug levels obtained at 8 to 16 hrs post-dose.
* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.

Definitions: b.i.d. = twice daily; d = day; wk = week; yr = year; qHS = every night; NC = No Change.

Effect of KALETRA on Co-administered Drugs

Table 17 - Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA (See Table 15 for Recommended Alterations in Dose or Regiment)

Co-administered Drug	Dose of Co-administered Drug (mg), Duration	Dose of KALETRA (mg), Duration	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Antiepileptic						
Lamotrigine	100 b.i.d., 12 d vs. 100 b.i.d., 8 d alone	400/100 capsule b.i.d., 12 d	18	0.54 (0.49, 0.58)	0.5 (0.47, 0.54)	0.44 (0.40, 0.47)
	200 b.i.d., 9 d vs. 100 b.i.d., 8 d alone	400/100 capsule b.i.d., 9 d	15	1.03 (0.90, 1.17)	0.91 (0.82, 1.02)	0.79 (0.69, 0.90)
Antifungal						
Ketoconazole	200 single dose	400/100 capsule b.i.d., 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Antimycobacterial						
Rifabutin	300 daily, 10 d alone vs. 150 daily, 10 d combo	400/100 capsule b.i.d., 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[a]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
HCV-Antiviral Agents						
Boceprevir	800 mg q8h, 6 d	400/100 tablet b.i.d., 22 d	39	0.50 (0.45, 0.55)	0.55 (0.49, 0.61)	0.43 (0.36, 0.53)
Telaprevir	750 mg q8h, 10 d	400/100 b.i.d., 20 d	12	0.47 (0.41, 0.52)	0.46 (0.41, 0.52)	0.48 (0.40, 0.56)

Co-administered Drug	Dose of Co-administered Drug (mg), Duration	Dose of KALETRA (mg), Duration	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
HIV-Antiviral Agents						
Efavirenz	600 qHS, 9 d	400/100 capsule b.i.d., 9 d	11, 12 *	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Fosamprenavir[b]	700 b.i.d. + ritonavir 100 b.i.d., 14 d	400/100 capsule b.i.d., 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir[c]	800 t.i.d., 5 d alone fasting vs. 600 b.i.d., 10 d with KALETRA non-fasting	400/100 capsule b.i.d., 15 d	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Maraviroc	300 mg b.i.d	400/100 capsule b.i.d.	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)
Nelfinavir[c]	1250 b.i.d., 14 d alone vs. 1000 b.i.d., 10 d combo	400/100 capsule b.i.d., 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 daily, 14 d, b.i.d., 6 d	400/100 capsule b.i.d., 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
				See **Table 15** for discussion of interaction.		
Saquinavir[c]	1200 t.i.d., 5 d alone vs. 800 b.i.d., 10 d with KALETRA	400/100 capsule b.i.d., 15 d	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
	800 b.i.d., 10 d with KALETRA vs. 1200 b.i.d., 5 d with KALETRA			0.984 (0.74, 1.30)	0.974 (0.73, 1.28)	0.95[d] (0.70, 1.29)

Co-administered Drug	Dose of Co-administered Drug (mg), Duration	Dose of KALETRA (mg), Duration	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Tenofovir[e]	300 mg daily, 14 d	400/100 capsule b.i.d., 14 d	24	NC	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)
HMG-CoA Reductase Inhibitors						
Atorvastatin	20 daily, 4 d	400/100 capsule b.i.d., 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Pravastatin	20 daily, 4 d	400/100 capsule b.i.d., 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rosuvastatin[f]	20 mg daily, 7 d	400/100 tablet b.i.d., 7 d	15	4.66 (3.4, 6.4)	2.08 (1.66, 2.6)	1.04 (0.9, 1.2)
Opioid Agonist						
Methadone	5 single dose	400/100 capsule b.i.d., 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	NA
Oral or Patch Contraceptive						
Ethinyl Estradiol	35 mcg daily, 21 d (norethindrone-mestranol)	400/100 capsule b.i.d., 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Norethindrone	1 daily, 21 d (norethindrone-mestranol)	400/100 capsule b.i.d., 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Tricyclic antidepressants						
Desipramine[g]	100 single dose	400/100 capsule b.i.d., 10 d	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	N/A

Co-administered Drug	Dose of Co-administered Drug (mg), Duration	Dose of KALETRA (mg), Duration	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated. Drug interaction studies were not performed with the once daily regimen of KALETRA. a. Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite. b. Data extracted from the fosamprenavir labeling. c. Ratio of parameters for indinavir, nelfinavir and saquinavir are not normalized for dose. d. Ratios are for saquinavir 1200 twice daily + KALETRA vs. saquinavir 800 twice daily + KALETRA. e. Data extracted from the tenofovir labelling. f. Data extracted from the rosuvastatin package insert and results presented at the 2007 Conference on Retroviruses and Opportunistic Infection (Hoody, et al., abstract L-107, poster # 564). g. Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism. * Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone. Definitions: b.i.d. = twice daily; d = day; wk = week; yr = year; qHS = every night; N/A = Not Available; NC = No Change.						

9.5 Drug-Food Interactions

The bioavailability of KALETRA tablets is not significantly affected when administered with a high or moderate fat meal (see **10.3 Pharmacokinetics**). KALETRA tablets can be taken with or without food.

The bioavailability of KALETRA oral solution is affected when administered with a high or moderate fat meal (see **10.3 Pharmacokinetics**). KALETRA oral solution must be taken with food.

9.6 Drug-Herb Interactions

Concomitant use of KALETRA and St. John's Wort (*Hypericum perforatum*), or products containing St. John's Wort, is contraindicated (see **2 CONTRAINDICATIONS**). Co-administration of protease inhibitors, including KALETRA, with St. John's Wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of virologic response and possible resistance to lopinavir or to the class of protease inhibitors.

9.7 Drug-Laboratory Test Interactions

The interactions of KALETRA with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the *Gag-Pol* polyprotein, resulting in the production of immature, non-infectious viral particles. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. The antiviral activity of KALETRA is due to lopinavir.

10.2 Pharmacodynamics

Viral Effects

Lopinavir is virologically 10-fold more active than ritonavir, with an EC_{50} of 0.07 mcg/mL against HIV-1_{IIIB} activity in MT4 cells in a medium containing 50% human serum and 10% calf serum. The protein binding corrected EC_{50} against wild-type HIV for ritonavir under the same conditions is 0.9 mcg/mL. Against ritonavir-resistant HIV, lopinavir displays potency similar to that observed by ritonavir against wild-type HIV. In the Phase 2 and Phase 3 trials, lopinavir has been tested in HIV PI-naïve subjects, as well as HIV-infected subjects with single PI experience who have developed various degrees of genotypic and phenotypic resistance to PIs and to NRTIs. Pharmacokinetic/pharmacodynamic modelling of the antiviral effect of lopinavir in these studies has shown little relationship between exposure and virologic outcome. In a study that evaluated subjects who were multiple PI-experienced, the C_{trough} to EC_{50} (of the pre-treatment HIV viral isolate) ratio was determined to be an important factor for durable virologic suppression with lopinavir/ritonavir.

The incidence of diarrhea showed increased rates with increased dose within individual studies; however, no statistically significant dose group differences were observed. Also, no apparent difference was observed in the incidence of diarrhea between the antiretroviral-naïve and experienced groups. The incidence of nausea was higher for treatment-naïve subjects who received the KALETRA capsule 400/200 mg dose than subjects who received the 400/100 mg dose. In addition, across-study comparisons suggested that naïve subjects receiving a KALETRA capsule 400/200 mg dose tended to have higher incidence rates of nausea compared to experienced subjects receiving the same dose.

Effects on the Electrocardiogram

A Phase 1, multiple-dose, open-label, placebo and active controlled (moxifloxacin 400 mg once daily), randomized study was conducted according to a four-way crossover design in healthy volunteers. Two dosage regimens of lopinavir/ritonavir were examined, a therapeutic dose of 400/100 mg twice daily and a supratherapeutic dose of 800/200 mg twice daily. Digital electrocardiograms (EKGs/ECGs) were performed in triplicate on study Day 3 and compared to time-matched baseline EKGs. On Day 3, lopinavir concentrations were approximately 1.5- to 3-fold higher than those observed at steady state with the 400/100 mg twice daily or the 800/200 mg once daily dose. At these increased concentrations, the maximum increase in QTcF was 3.6 msec with an upper 95% CI of 6.3 msec for 400/100 mg twice daily, and 13.1 msec with an upper bound 95% CI of 15.8 msec for supratherapeutic dose of 800/200 mg twice daily. Exposure-response analysis were conducted with both lopinavir and ritonavir concentrations as they contributed equally to the QTc effect, the model predicted no effect (the 95% upper CI of QTcF interval less than 10 msec) up to combined lopinavir and ritonavir concentrations approximately 35 to 70% higher than maximum concentrations observed with 400/100 mg twice daily or 800/200 mg once daily dosing. Therefore, lopinavir/ritonavir at approved doses is unlikely to result in clinically significant QTcF prolongation.

The absolute PR interval on Day 3 and change from baseline were also evaluated. Mean change from baseline in PR interval of 11.6 to 31.2 msec was noted in subjects receiving KALETRA up to a supratherapeutic dose of 800/200 mg twice daily on study Day 3. The maximum PR interval was 286 msec and no second or third degree heart block was observed. Exposure-response analysis predicted that the PR effect of lopinavir/ritonavir plateaus around 20 msec, thus lopinavir/ritonavir 400/100 mg twice daily is unlikely to result in clinically significant PR prolongation.

10.3 Pharmacokinetics

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the 2 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 capsules 400/100 mg twice daily yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-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.

At steady state, KALETRA capsules 400/100 mg twice daily taken without meal restrictions produced a mean ± SD (standard deviation) lopinavir C_{max} of 9.6 ± 4.4 mcg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 mcg/mL. Lopinavir AUC over a 12-hour dosing interval averaged 82.8 ± 44.5 mcg•h/mL. Administration of a single 400/100 mg dose of KALETRA capsules with a moderate-fat meal (500 to 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. To enhance bioavailability and minimize pharmacokinetic variability, KALETRA capsules should be taken with food. The half-life ($t_{½}$) of lopinavir over a 12-hour dosing interval averaged 5 to 6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 L/h.

Absorption

In a pharmacokinetic study in HIV-positive subjects (n=19), multiple dosing with 400/100 mg KALETRA capsules twice daily with food for 3 weeks produced a mean ± SD lopinavir C_{max} of 9.8 ± 3.7 mcg/mL (95% CI: 8.0 to 11.6 mcg/mL), occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 mcg/mL (95% CI: 5.7 to 8.5 mcg/mL) and minimum concentration within a dosing interval was 5.5 ± 2.7 mcg/mL (95% CI: 4.2 to 6.8 mcg/mL). Lopinavir AUC over a 12-hour dosing interval averaged 92.6 ± 36.7 mcg•h/mL (95% CI: 74.9 to 110.3 mcg•h/mL). The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under non-fasting 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 Cmax of lopinavir were 22% lower for the KALETRA oral solution relative to the capsule formulation.

The relative bioavailability of KALETRA 200/50 mg tablets compared to KALETRA capsules was assessed in two Phase 1, single-center, open-label, randomized, cross-over studies (Studies M03-616 and M04-703) in 111 healthy adults under fed conditions (moderate-fat meal, 490 to 560 Kcal, 20 to 30% of calories from fat) as a single 400/100 mg dose. Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg KALETRA tablets are similar to three 133.3/33.3 mg KALETRA capsules under fed conditions with less pharmacokinetic variability. Following a moderate-fat meal, relative to the KALETRA capsule, administration of KALETRA 200/50 mg tablets increased lopinavir AUC_t and C_{max} by 18 and 24%, respectively, and increased ritonavir AUC_t and C_{max} by 20 and 35%, respectively.

In a Phase 1, single-center, open-label, randomized, cross-over study (Study M03-616) in 63 healthy adults (46 males, 17 females), no clinically significant changes in C_{max} and AUC were observed following the administration of a single 400/100 mg dose of KALETRA 200/50 mg tablets under fasting conditions or following a moderate-fat meal (558 Kcal, 24.1% from fat) or a high-fat meal (998 Kcal, 51.3% from fat) relative to the KALETRA capsule dose following a moderate-fat meal. Relative to the KALETRA

capsule dose following a moderate-fat meal, administration of KALETRA 200/50 mg tablets under fasting conditions increased lopinavir C_{max} by 10% with no change in AUC_t, and increased ritonavir AUC_t and C_{max} by 10 and 33%, respectively. Relative to the KALETRA capsule dose following a moderate-fat meal, administration of KALETRA 200/50 mg tablets following a moderate-fat meal increased lopinavir AUC_t and C_{max} by 27 and 30%, respectively, and increased ritonavir AUC_t and C_{max} by 27 and 40%, respectively. Relative to the KALETRA capsule dose following a moderate-fat meal, administration of KALETRA 200/50 mg tablets following a high-fat meal showed no change in lopinavir AUC_t and C_{max}, and increased ritonavir AUC_t and C_{max} each by 15%.

In a Phase 1, single-center, open-label, randomized, cross-over study (Study M04-703) in 48 healthy adults (34 males, 14 females) following a moderate-fat meal (492 Kcal, 22.9% from fat) and a single 400/100 mg dose, the relative bioavailability of KALETRA 200/50 mg tablets from 2 production lots compared to KALETRA capsules was increased for lopinavir AUC_t and C_{max} by 10 to 13% and 17 to 23%, respectively and increased for ritonavir AUC_t and C_{max} by 15% and 29 to 38%, respectively.

In a Phase 3, multicenter, open-label, randomized study (Study M05-730) in 664 HIV-1 infected adult subjects (502 males, 144 females), following multiple-dose administration of KALETRA in a parallel group comparison of Week 2 data (n=18 for twice daily and n=17 for once daily), lopinavir concentrations are approximately 14 to 25% higher following twice daily administration of the tablet compared to the capsule and 19 to 38% higher following once daily administration of the tablet compared to the capsule. Ritonavir plasma levels were similarly increased 25 to 54% following twice daily and once daily dosing of the KALETRA tablet compared to the capsule. In a within-subject analysis comparing the tablet at Week 10 to the capsule at Week 2 (n=18 for twice daily and n=16 for once daily), lopinavir and ritonavir plasma levels did not appear to be clinically significantly increased. The maximum average changes following twice daily and once daily dosing were 4 and 16%, respectively, for lopinavir and 10 and 18%, respectively, for ritonavir.

The relative bioavailability of KALETRA 100/25 mg tablets compared to KALETRA 200/50 mg tablets was assessed in a Phase 1, single-center, open-label, randomized, cross-over study (Study M06-858) in 44 healthy adults (35 males, 9 females) under fasting conditions as a single 400/100 mg dose. Plasma concentrations of lopinavir and ritonavir after administration of four 100/25 mg KALETRA tablets are similar to two 200/50 mg KALETRA tablets under fasting conditions.

Effects of Food on Oral Absorption

KALETRA Tablets

The relative bioavailability of KALETRA 200/50 mg tablets under fasting conditions was compared to KALETRA 200/50 mg tablets following meals in a Phase 1, single-center, open-label, randomized, cross-over study (Study M03-616) in 63 healthy adults as a 400/100 mg dose. No clinically significant changes in C_{max} and AUC were observed following administration of KALETRA 200/50 mg tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of KALETRA 200/50 mg tablets with a moderate-fat meal (558 Kcal, 24.1% calories from fat) increased lopinavir AUC_t and C_{max} by 26.9 and 17.6%, respectively, and ritonavir AUC_t and C_{max} by 15.6 and 4.9%, respectively. Relative to fasting, administration of KALETRA 200/50 mg tablets with a high-fat meal (998 Kcal, 51.3% from fat) increased lopinavir AUC_t by 18.7% but not C_{max}, and ritonavir AUC_t and C_{max} were increased 24.7 and 10.3%, respectively. The average lopinavir T_{max} for the 200/50 mg tablet under fasting conditions, following a moderate-fat meal and following a high-fat meal were 3.6, 4.0 and 5.4 hours, respectively. The average ritonavir T_{max} for the 200/50 mg tablet under fasting conditions, following a moderate-fat meal and following a high-fat meal were 3.4, 4.0 and 5.4 hours, respectively. The lopinavir terminal

phase half-lives were similar for all regimens and ranged, on average, from 2.6 to 2.7 hours. The ritonavir terminal phase half-lives were similar for all regimens and ranged, on average, from 4.2 to 4.7 hours. Additional details regarding the pharmacokinetics of the KALETRA capsule and 200/50 mg tablet formulations under various meal conditions may be found in **10.3 Pharmacokinetics**. KALETRA tablets may therefore be taken with or without food.

KALETRA Oral Solution

Relative to fasting, KALETRA oral solution dosed with a moderate-fat meal (500 to 683 Kcal, 23 to 25% calories from fat) in healthy adults was associated with increases in lopinavir AUC and C_{max} of 80 and 54%, respectively. Relative to fasting, administration of KALETRA oral solution with a high-fat meal (872 Kcal, 56% from fat) increased lopinavir AUC and C_{max} by 130 and 56%, respectively. To enhance bioavailability and minimize pharmacokinetic variability, KALETRA oral solution should be taken with food.

Distribution

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

After a single dose of [^{14}C]lopinavir/ritonavir (10/5 mg/kg) in rats, the radioactivity was distributed well throughout the body. With the exception of the adrenal gland, thyroid gland, liver and gastrointestinal tract, at 4 hours the tissue to plasma ratios of the remaining tissues were less than one. The highest concentrations were found in the liver and the lowest concentrations in the brain. The brain concentrations were approximately equal to the free concentrations in the plasma (approximately 2%). Concentrations in the lymphatic system were 6 to 61% of those in the plasma.

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/hr (mean ± SD, n=19).

Once Daily Dosing

The pharmacokinetics of once daily KALETRA have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. KALETRA capsules 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 capsules once daily for 4 weeks with food (n=24) produced a mean ± SD lopinavir C_{max} of 11.8 ± 3.7 mcg/mL, occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 3.2 ± 2.1 mcg/mL and minimum concentration within a dosing interval was 1.7 ± 1.6 mcg/mL. Lopinavir AUC over a 24-hour dosing interval averaged 154.1 ± 61.4 mcg•h/mL.

Special Populations and Conditions

- **Pediatrics**

  KALETRA Oral Solution

  The pharmacokinetics of KALETRA oral solution 300/75 mg/m^2 twice daily and 230/57.5 mg/m^2 twice daily have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine) (see **14.2 Study Results**).

  The following describes the KALETRA - nevirapine interaction. The nevirapine regimen was 7 mg/kg twice daily (6 months to 8 years) or 4 mg/kg twice daily (> 8 years). The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1, 8.2 ± 2.9 and 3.4 ± 2.1 mcg/mL respectively, after KALETRA 230/57.5 mg/m^2 twice daily without nevirapine (n=12), and were 85.8 ± 36.9, 10.0 ± 3.3 and 3.6 ± 3.5 mcg/mL respectively, after 300/75 mg/m^2 twice daily with nevirapine (n=12).

  KALETRA Tablets

  The KONCERT/PENTA 18 study assessed pharmacokinetics, safety and efficacy of twice daily versus once daily KALETRA tablets dosed as part of combination therapy in HIV-1 infected children. The pharmacokinetic substudy of KONCERT/PENTA18 explored lopinavir exposure in patients randomized to KALETRA tablets dosed either twice daily or once daily for 4 weeks stratified by body weight band (≥ 15 to ≤ 25 kg, > 25 to ≤ 35 kg, > 35kg). At enrollment, participating children were on combination antiretroviral regimen that included KALETRA and had viral suppression (HIV-1 RNA < 50 copies/mL) for at least the prior 24 weeks. The lopinavir mean steady-state AUC_{24}, C_{max}, and C_{last} were 237.3 ± 86.4, 13.0 ± 4.1 and 6.5 ± 3.3 mcg/mL respectively, after KALETRA tablets dosed twice daily (n=26), and were 171.5 ± 60.2, 14.5 ± 3.5 and 1.9 ± 1.9 mcg/mL respectively, after KALETRA tablets dosed once daily (n=26) (see **14.2 Study Results**).

- **Geriatrics**

  Lopinavir pharmacokinetics has not been studied in elderly patients.

- **Sex**

  No gender-related pharmacokinetic differences have been observed in adult patients. Population pharmacokinetic analysis of lopinavir in HIV-infected subjects indicated that gender had no apparent effect on the exposure to lopinavir.

- **Ethnic Origin**

  No clinically important pharmacokinetic differences due to race have been identified.

Population pharmacokinetic analysis of lopinavir in HIV-infected subjects indicated that race had no apparent effect on the exposure to lopinavir.

- **Hepatic Insufficiency**

  Lopinavir is principally metabolized and eliminated by the liver. Multiple dosing of KALETRA capsules 400/100 mg twice daily to HIV 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 Cmax compared to HIV-infected subjects with normal hepatic function (n=12). Additionally, the plasma protein binding of lopinavir was 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 **7 WARNINGS AND PRECAUTIONS**).

- **Renal Insufficiency**

  Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since less than 3% of the dose of lopinavir is eliminated unchanged in the urine, a decrease in total body clearance is not expected in patients with renal insufficiency. Population pharmacokinetic analysis of lopinavir in HIV-infected subjects indicated that subjects with mild renal impairment (CL_{CR} between 50 to 80 mL/min, n=79) had no apparent effect on the exposure to lopinavir.

11 STORAGE, STABILITY AND DISPOSAL

Temperature:

KALETRA Film-Coated Tablets

Store KALETRA film-coated tablets between 15 and 30°C. It is recommended that the product be stored and dispensed in the original container.

KALETRA Oral Solution

Store KALETRA oral solution between 2 and 8°C until dispensed. Avoid exposure to excessive heat. Keep cap tightly closed. Product must be stored and dispensed in the original container. Refrigeration of KALETRA oral solution by the patient is not required if used within 42 days and stored below 25°C.

Others:

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

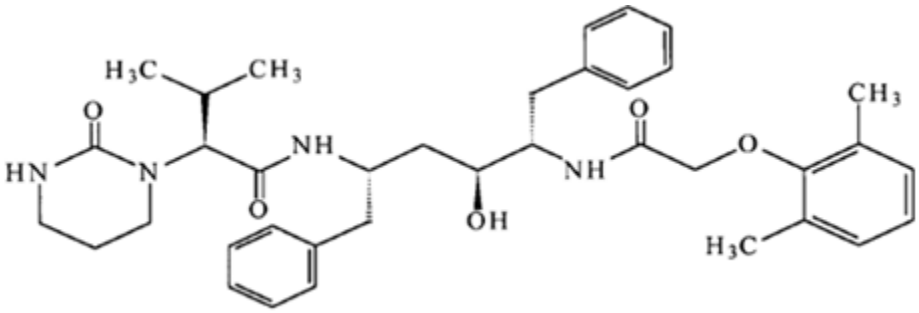
Drug Substance

Proper name: Lopinavir

Chemical name: [1S-[1R*,(R*), 3R*, 4R*]]-N-[4-[[2,6-dimethylphenoxy) acetyl] amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide

Molecular formula and molecular mass: $C_{37}H_{48}N_4O_5$ and 628.80 g/mol

Structural formula:



Physicochemical properties: Lopinavir is a white to light tan powder. Lopinavir is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

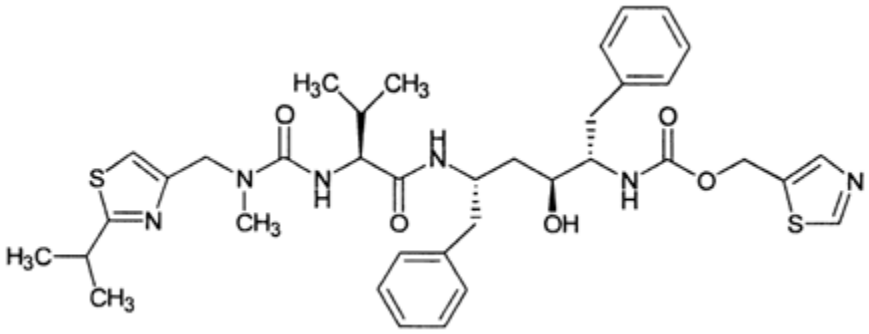
Drug Substance

Proper name: Ritonavir

Chemical name: 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, [5S-(5R*,8R*,10R*,11R*)]

Molecular formula and molecular mass: $C_{37}H_{48}N_6O_5S_2$ and 720.95 g/mol

Structural formula:



Physicochemical properties: Ritonavir is a white to light tan powder. Ritonavir has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 18 - Summary of Patient Demographics for Clinical Trials in Specific Indications

	Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Mean Age (Range)[a]	Gender Race (%M/F) (%C/O)[b]	Mean Baseline CD_4 Cell Count (Range)[c]	Mean Baseline Plasma HIV-1 RNA (Range)[d]
Patients Without Prior Antiretroviral Therapy	M98-863	Randomized, Double-blinded, Multicenter	KALETRA capsules (400/100 mg b.i.d.) + stavudine + lamivudine vs. nelfinavir (750 mg t.i.d.) + stavudine + lamivudine Oral 48 weeks	653	38 (19-84)	80/20 7/43	259 (2-949)	4.9 (2.6-6.8)
	M97-720 (Evaluation KALETRA at 3 dose levels)	Randomized, Blinded, Multicenter	GRP I - KALETRA capsules (200/100 mg b.i.d.) + stavudine + lamivudine GRP II - KALETRA capsules (400/100 mg b.i.d. & 400/200 mg b.i.d.) + stavudine + lamivudine Oral 360 weeks	100	35 (21-59)	96/4 70/30	338 (3-918)	4.9 (3.3-6.3)
	M02-418	Randomized, Open-label, Multicenter	KALETRA capsules daily + tenofovir DF + emitricitabine vs. KALETRA capsules b.i.d. + tenofovir DF + emitricitabine Oral 48 weeks	190	39 (19-75)	78/22 54/46	260 (3-1006)	4.8 (2.6-6.4)

	Study #	Trial Design	Dosage, Route of Administration and Duration		Study Subjects	Mean Age (Range)[a]	Gender Race (%M/F) (%C/O)[b]	Mean Baseline CD_4 Cell Count (Range)[c]	Mean Baseline Plasma HIV-1 RNA (Range)[d]
Patients With Prior Antiretroviral Therapy	M98-888	Randomized, Open-label, Multicenter	KALETRA capsules (400/100 mg b.i.d.) + nevirapine & NRTIs vs. investigator-selected PI(s) + nevirapine + NRTIs Oral 48 weeks		288	40 (18-73)	86/14 68/32	322 (10-1059)	4.1 (2.6-6.0)
	M97-765 (Evaluation lopinavir/ ritonavir at 2 dose levels)	Randomized, Blinded, Multicenter	KALETRA capsules (400/100 mg b.i.d. & 400/200 mg b.i.d.) + nevirapine & 2 NRTIs Oral 144 weeks		70	40 (22-66)	90/10 73/27	372 (72-807)	4.0 (2.9-5.8)
Pediatric Use	M98-940	Open-label, Multicenter	Randomized Oral 72 weeks	KALETRA oral solution (230/57.5 mg per m^2) KALETRA oral solution (300/75 mg per m^2)	100 (40% anti-retroviral naïve & 56% experienced)	5 (6 months to 12 yrs) (14% < 2 yrs)	43/57 14/86	838	4.7
	KONCERT/ PENTA 18	Randomized, Open-label, Multicenter	Stratified by body weight band Oral 48 weeks	KALETRA tablets ≥ 15 to ≤ 25 kg 400/100 mg once daily vs. divided b.i.d > 25 to ≤ 35 kg 600/150 mg once daily vs. divided b.i.d > 35 kg 800/200 mg once daily vs. divided b.i.d	173	11 (4-18)	46/54 25/74	937 (267-2368)	2.0 (1.7-4.9)[e]

	Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Mean Age (Range)[a]	Gender Race (%M/F) (%C/O)[b]	Mean Baseline CD_4 Cell Count (Range)[c]	Mean Baseline Plasma HIV-1 RNA (Range)[d]
a. Measured in Years b. % Male/Female, % Caucasian/Other c. Measured in cells/mm^3 d. Measured in log_{10} copies/mL e. Median and range provided for 16 subjects with HIV-1 RNA ≥50 copies/mL; all other subjects had baseline HIV-1 RNA < 50 copies/mL. Definitions: b.i.d. = twice daily; t.i.d. = three times a day; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; GRP = Group.								

14.2 Study Results

Adult Use

Patients Without Prior Antiretroviral Therapy

Study M98-863: KALETRA capsules twice daily + stavudine + lamivudine compared to nelfinavir three times a day + stavudine + lamivudine

Study M98-863 was a randomized, double-blind, multicentre trial comparing treatment with KALETRA (lopinavir/ritonavir) capsules (400/100 mg twice daily) + stavudine and lamivudine versus nelfinavir (750 mg three times a day) + stavudine and lamivudine in 653 antiretroviral treatment-naïve patients. Patients had a mean age of 38 years (range: 19 to 84 years), 57% were Caucasian, and 80% were male. Mean baseline CD_4 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).

The percent of patients with HIV RNA < 400 copies/mL and outcomes of patients through 48 weeks are summarized in **Table 19**.

Table 19 - Outcomes of Randomized Treatment Through Week 48 (Study M98-863)

Outcome	KALETRA capsules 400/100 mg b.i.d. + d4T + 3TC (N=326)	Nelfinavir 750 mg t.i.d. + d4T + 3TC (N=327)
Responder[a]	75%	62%
Virologic Failure[b]	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse event	4%	4%
Discontinued for other reasons[c]	10%	8%

a. Patients achieved and maintained confirmed HIV RNA less than 400 copies/mL through Week 48.
b. Includes confirmed viral rebound and failure to achieve confirmed less than 400 copies/mL through Week 48.
c. Includes loss to follow-up, patient's withdrawal, non-compliance, protocol violation, and other reasons.
Definitions: b.i.d. = twice daily; t.i.d. = three times daily; d4T = stavudine; 3TC = lamivudine.

Through 48 weeks of therapy there was a statistically significant higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV RNA less than 400 copies/mL (75 vs. 62%, respectively) and HIV RNA less than 50 copies/mL (67 vs. 52%, respectively). Treatment response by baseline HIV RNA level subgroups is presented in **Table 20**.

Table 20 - Proportion of Responders Through Week 48 by Baseline Viral Load (Study M98-863)

Baseline Viral Load (HIV-1 RNA copies/mL)	KALETRA capsules 400/100 mg b.i.d. + d4T + 3TC			Nelfinavir t.i.d. + d4T + 3TC		
	< 400 copies/mL[a]	< 50 copies/mL[b]	n	< 400 copies/mL[a]	< 50 copies/mL[b]	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

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

b. Patients achieved HIV RNA < 50 copies/mL at Week 48.

Definitions: b.i.d. = twice daily; t.i.d. = three times daily; D4T = stavudine; 3TC = lamivudine.

Through 48 weeks of therapy, the mean increase from baseline in CD_4 cell count was 207 cells/mm^3 for the KALETRA arm and 195 cells/mm^3 for the nelfinavir arm.

Study M97-720: KALETRA capsules twice daily + stavudine + lamivudine

Study M97-720 was a randomized, blinded, multicentre trial evaluating treatment with KALETRA capsules at 3 dose levels (Group I: 200/100 mg twice daily and 400/100 mg twice daily; Group II: 400/100 mg twice daily and 400/200 mg twice daily) + lamivudine (150 mg twice daily) and stavudine (40 mg twice daily) in 100 antiretroviral-naïve patients. All patients were converted to open-label KALETRA capsules at the 400/100 mg twice daily dose between Weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59 years), 70% were Caucasian, and 96% were male. Mean baseline CD_4 cell count was 338 cells/mm^3 (range: 3 to 918 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 3.3 to 6.3 $\log_{10}$ copies/mL).

Through 360 weeks of treatment, the proportion of patients with HIV RNA < 400 (< 50) copies/mL was 61% (59%) [N=100] (see **Table 21**), and the corresponding mean increase in CD_4 cell count was 501 cells/mm^3 (see **Table 22**). Thirty-nine patients (39%) discontinued the study, including 15 (15%) discontinuations due to adverse events and 1 (1%) death. Eighteen (18%) patients demonstrated loss of virologic response (2 consecutive rebound HIV-1 RNA values above 400 copies/mL, 1 rebound HIV-1 RNA value followed by discontinuation, or failure to achieve HIV-1 RNA < 400 copies/mL). Genotypic analysis of viral isolates was conducted on these patients and an additional 10 patients with isolated HIV-1 RNA values > 400 copies/mL after Week 24. Results from 19 patients confirmed no primary or active site mutations in protease (amino acids at positions 8, 30, 32, 36, 47, 48, 50, 82, 84 and 90) or protease inhibitor (PI) phenotypic resistance.

Table 21 - Summary of HIV-1 RNA Results (Study M97-720)

	Proportion of Subjects with HIV-1 RNA Levels < 400 Copies/mL		Proportion of Subjects with HIV-1 RNA Levels < 50 Copies/mL	
Week	**On-Treatment**	**ITT (NC=F)**	**On-Treatment**	**ITT (NC=F)**
24	87/92 (95%)	90/100 (90%)	71/90 (79%)	74/100 (74%)
48	85/94 (90%)	85/100 (85%)	76/94 (81%)	76/100 (76%)
72	82/84 (98%)	87/100 (87%)	76/84 (91%)	79/100 (79%)
204	71/72 (99%)	71/100 (71%)	70/72 (97%)	70/100 (70%)
360	61/62 (98%)	61/100 (61%)	59/62 (95%)	59/100 (59%)
Definitions: ITT (NC=F): Intent-to-treat (Non-completer=Failure).				

Table 22 - Mean Change from Baseline to Week 360 in CD_4 Cell Count by Baseline Value (Study M97-720)

Baseline CD_4 Cell Count Value	N[a]	Baseline Mean (cells/microliter)	Week 360 Mean (cells/microliter)	Mean (SE) Change from Baseline to Week 360
< 50	15	22.8	555.6	532.8 (111.61)
50-199	12	121.8	597.8	476.1 (65.56)
200-349	11	272.0	745.5	473.5 (72.66)
350-499	11	408.7	1010.7	602.0 (84.13)
≥ 500	11	656.2	1065.9	409.7 (75.65)
a. Analysis includes all subjects with CD_4 cell count values at both baseline and Week 360; N=60. Definitions: SE = standard error				

Study M02-418: KALETRA capsules daily + tenofovir DF + emtricitabine compared to lopinavir/ritonavir twice daily + tenofovir DF + emtricitabine

Study M02-418 was a randomized, open-label, multicentre trial comparing treatment with KALETRA capsules 800/200 mg once daily + tenofovir DF and emtricitabine versus KALETRA capsules 400/100 mg twice daily + tenofovir DF and emtricitabine in 190 antiretroviral-naïve patients. Patients had a mean age of 39 years (range: 19 to 75 years), 54% were Caucasian, and 78% were male. Mean baseline CD_4 cell count was 260 cells/mm^3 (range: 3 to 1006 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.8 log_{10} copies/mL (range: 2.6 to 6.4 log_{10} copies/mL).

Treatment responses and outcomes of randomized treatment are presented in **Table 23** and **Table 24**, respectively. Through 48 weeks of treatment, the proportion of patients with HIV-1 RNA < 50 copies/mL was 71% (KALETRA once daily [N=115]) and 65% (KALETRA twice daily [N=75]).

Table 23 - Virologic response Through Week 48 (Study M02-418)[a,b]

Week	Proportion of Subjects Responding < 50 copies/mL ITT (FDA TLOVR)	
	KALETRA capsules 800/200 mg daily + TDF + FTC (N=115)	KALETRA capsules 400/100 mg b.i.d. + TDF + FTC (N=75)
4	6%	0%
8	18%	17%
16	40%	45%
24	58%	57%
32	68%	62%
40	72%	65%
48	71%	65%

a. Roche AMPLICOR HIV-1 MONITOR Assay

b. Responders at each visit are patients who had achieved and maintained HIV-1 RNA < 50 copies/mL without discontinuation by that visit.

Definitions: b.i.d. = twice daily; TDF = tenofovir DF; FTC = emtricitabine; ITT (FDA TLOVR) = Intent-to-treat (FDA Time to Loss of Virologic Response)

Table 24 - Outcomes of Randomized Treatment Through Week 48 (Study M02-418)

Outcome	KALETRA capsules 800/200 mg daily + TDF + FTC (N=115)	KALETRA capsules 400/100 mg b.i.d. + TDF + FTC (N=75)
Responder*[a]	71%	65%
Virologic failure[b]	10%	9%
Rebound	6%	5%
Never suppressed though 48 Weeks	3%	4%
Death	0%	1%
Discontinued due to adverse event	12%	7%
Discontinued for other reasons[c]	7%	17%

* Corresponds to rates at Week 48 in **Table 23**.

a. Patients achieved and maintained confirmed HIV RNA < 50 copies/mL through Week 48.

b. Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48.

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

Definitions: b.i.d. = twice daily; TDF = tenofovir DF; FTC = emtricitabine.

Through 48 weeks of therapy, 71% of the patients in the KALETRA capsules daily arm and 65% of the patients in the KALETRA twice daily arm achieved and maintained HIV RNA < 50 copies/mL (95% confidence interval for the difference, -7.6 to 19.5%). Mean CD_4 cell count increases at Week 48 were 185 cells/mm^3 for the KALETRA daily arm and 196 cells/mm^3 for the KALETRA twice daily arm.

Study M05-730: KALETRA tablets once daily + tenofovir DF + emtricitabine compared to KALETRA tablets twice daily + tenofovir DF + emtricitabine

Study M05-730 was a randomized, open-label, multicenter trial comparing treatment with KALETRA 800/200 mg once daily + tenofovir DF and emtricitabine versus KALETRA 400/100 mg twice daily + 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 CD_4+ 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 *25***.

Table 25 - Outcomes of Randomized Treatment Through Week 48 (Study M05-730)

Outcome[a]	KALETRA tablets 800/200 mg daily + TDF + FTC (N=333)	KALETRA tablets 400/100 mg b.i.d. + TDF + FTC (N=331)
Responder[b]	78 %	77 %
Virologic failure[c]	10 %	9 %
Rebound	5 %	5 %
Never suppressed and on study at 48 Weeks	5 %	2 %
Discontinued due to insufficient viral response	1 %	2 %
Death	1 %	0 %
Discontinued due to adverse event	4 %	3 %
Discontinued for other reasons[d]	8 %	12 %

a. Based on FDA Time to Loss of Virologic Response algorithm, a secondary endpoint for the study.
b. Patients achieved and maintained confirmed HIV RNA < 50 copies/mL through Week 48.
c. Includes confirmed viral rebound, failure to suppress and on study at Week 48, and discontinued due to insufficient viral response.
d. Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Definitions: b.i.d. = twice daily; TDF = tenofovir DF; FTC = emtricitabine

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 per the FDA Time to Loss of Virologic Response algorithm. The difference in response rates between groups was 0.4% (95% confidence interval for the difference, -5.9% to 6.8%); this difference was not statistically significant (p = 0.926). Mean CD_4+ 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.

Patients with Prior Antiretroviral Therapy

Study M98-888: KALETRA capsules twice daily + nevirapine + NRTIs compared to investigator-selected PI(s) + nevirapine + NRTIs

Study M98-888 was a randomized, open-label, multicentre trial comparing treatment with KALETRA capsules (400/100 mg twice daily) + nevirapine and NRTIs versus investigator-selected PI(s) + nevirapine and NRTIs in 288 single PI-experienced non-nucleoside reverse transcriptase inhibitor (NNRTI)-naïve patients. Patients had a mean age of 40 years (range: 18 to 73 years), 68% were Caucasian, and 86% were male. Mean baseline CD_4 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 26**.

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

Through 48 weeks of therapy, the mean increase from baseline in CD_4 cell count was 111 cells/mm^3 for the KALETRA capsules arm and 112 cells/mm^3 for the investigator-selected PI(s) arm.

Table 26 - Outcomes of Randomized Treatment Through Week 48 (Study M98-888)

Outcome	KALETRA capsules 400/100 mg b.i.d. + nevirapine + NRTIs (N=148)	Investigator-selected PI(s) + nevirapine + NRTIs (N=140)
Responder*[a]	57%	33%
Virologic failure[b]	24%	41%
Rebound	11%	19%
Never suppressed though Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse event	5%	11%
Discontinued for other reasons[c]	14%	13%

Outcome	KALETRA capsules 400/100 mg b.i.d. + nevirapine + NRTIs (N=148)	Investigator-selected PI(s) + nevirapine + NRTIs (N=140)
* Corresponds to responses at Week 48.		
a. Patients achieved and maintained confirmed HIV RNA < 400 copies/mL through Week 48.		
b. Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.		
c. Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.		
Definition: b.i.d. = twice daily; NRTIs= nucleoside reverse transcriptase inhibitors; PI = protease inhibitor.		

Study M97-765: KALETRA capsules twice daily + nevirapine + NRTIs

Study M97-765 was a randomized, blinded, multicentre trial evaluating treatment with KALETRA capsules at 2 dose levels (400/100 mg twice daily and 400/200 mg twice daily) + nevirapine (200 mg twice daily) and 2 NRTIs in 70 single PI-experienced, NNRTI-naïve patients. Patients had a mean age of 40 years (range: 22 to 66 years), were 73% Caucasian, and were 90% male. Mean baseline CD_4 cell count was 372 cells/mm^3 (range: 72 to 807 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.0 log_{10} copies/mL (range: 2.9 to 5.8 log_{10} copies/mL).

Through 144 weeks of treatment in Study M97-765, the proportion of patients with RNA < 400 (< 50) copies/mL was 54% (50%) [n=70], and the corresponding mean increase in CD_4 cell count was 212 cells/mm^3. Twenty-seven patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

Study M06-802: KALETRA tablets 800/200 mg once daily versus 400/100 mg twice daily when co-administered with NRTIs in antiretroviral-experienced, HIV-1 infected subjects

Study 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. 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 2 NRTIs 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 CD_4 cell count was 254 cells/mm^3 (range: 4 to 952 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.3 log_{10} copies/mL (range: 1.7 to 6.6 log_{10} copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in **Table *27***.

Table 27 - Outcomes of Randomized Treatment Through Week 48 (Study M06-802)

Outcome	KALETRA Once Daily + NRTIs (n=300)	KALETRA Twice Daily + NRTIs (n=299)
Responder[a]	55%	52%
Virologic failure[b]	25%	28%
Rebound	12%	14%
Never suppressed though Week 48	13%	15%
Death	1%	1%
Discontinued due to adverse event	4%	6%
Discontinued for other reasons[c]	15%	14%

a. Patients achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48.
b. Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48.
c. Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.
Definitions: NRTI = Nucleoside/Nucleotide reverse transcriptase inhibitor.

Pediatric Use

Study M98-940: KALETRA oral solution twice daily in antiretroviral-naïve and experienced pediatric patients

Study M98-940 was an open-label, multicentre trial evaluating the pharmacokinetic profile, tolerability, safety, and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral-naïve (44%) and experienced (56%) pediatric patients. All patients were NNRTI-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 + up to 2 NRTIs.

Safety, efficacy and pharmacokinetic profiles of the 2 dose regimens were assessed after 3 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 CD_4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 72 weeks of therapy, the proportion of patients who achieved and maintained HIV RNA < 400 copies/mL was 75% (33/44) for antiretroviral-naïve patients, 72% (23/32) for NRTI only experienced patients and 50% (12/24) for PI- and NRTI-experienced patients. The mean increase from baseline in CD_4 cell count was 387 cells/mm^3 for antiretroviral-naïve and 435 cells/mm^3 for antiretroviral-experienced patients treated through 72 weeks. Two patients (2%) prematurely discontinued the study due to an adverse event or HIV-related event. One antiretroviral-naïve patient prematurely discontinued secondary to an adverse event attributed to KALETRA. One antiretroviral-experienced patient prematurely discontinued secondary to an HIV-related event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine).

Study KONCERT/PENTA 18: KALETRA tablets 100/25 mg twice daily versus once daily dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children

Study KONCERT/PENTA 18 was a prospective multicenter, randomized, open-label study that evaluated the pharmacokinetic profile, efficacy, and safety of twice daily versus once daily dosing of KALETRA 100/25 mg 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, the efficacy and safety with twice daily dosing (n=87) in the pediatric population given KALETRA 100/25 mg tablets was consistent with the efficacy and safety findings in previous adult and pediatric studies using KALETRA twice daily (see **0 ACTION AND PHARMACOLOGY**).

15 MICROBIOLOGY

Antiviral activity in vitro

The in vitro antiviral activity of lopinavir against laboratory HIV strains and clinical HIV 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}) of lopinavir against 5 different HIV-1 laboratory strains ranged from 10 to 27 nM (0.006 to 0.017 mcg/mL, 1 mcg/mL = 1.6 microM) and ranged from 4 to 11 nM (0.003 to 0.007 mcg/mL) against several HIV-1 subtype B clinical isolates (n=6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these 5 laboratory strains ranged from 65 to 289 nM (0.04 to 0.18 mcg/mL), representing a 7-to 11-fold attenuation.

Resistance

The selection of resistance to KALETRA therapy in antiretroviral treatment-naïve patients has not yet been characterized. In a Phase 3 study of 653 antiretroviral treatment naïve patients (Study M98-863), plasma viral isolates from each patient on treatment with plasma HIV > 400 copies/mL at Week 24, 32, 40 and/or 48 were analysed. 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 D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to KALETRA in antiretroviral-naïve pediatric patients (Study M98-940) appears to be consistent with that seen in adult patients (Study M98-863).

There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. However, in Phase 2 studies of 227 antiretroviral treatment-naïve and PI-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. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir)

and 1 patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All 4 of these patients had at least 4 mutations associated with PI resistance immediately prior to KALETRA therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which were recognized to be associated with PI resistance.

Cross-resistance

Preclinical Studies

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

The in vitro activity of lopinavir against clinical isolates from patients previously treated with a single PI was determined. Isolates that displayed > 4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed < 4-fold reduced susceptibility to lopinavir. Isolates with > 4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7 to 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with 2 or more PIs showed greater reductions in susceptibility to lopinavir, as described in the Clinical Studies section that follows.

Clinical Studies - Antiviral activity of KALETRA in patients with previous protease inhibitor (PI) therapy.

The clinical relevance of reduced in vitro susceptibility to lopinavir has been examined by assessing the virologic response to KALETRA therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naïve patients with HIV RNA > 1000 copies/mL despite previous therapy with at least 2 PIs selected from nelfinavir, indinavir, saquinavir and ritonavir (Study M98-957). In this study, patients were initially randomized to receive 1 of 2 doses of KALETRA in combination with efavirenz and nucleoside reverse transcriptase inhibitors (NRTIs). The EC_{50} of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC_{50} against wild type HIV. Fifty-five percent (31/56) of these baseline isolates displayed a > 4-fold reduced susceptibility to lopinavir with a mean reduction in lopinavir susceptibility of 27.9-fold.

Table 28 shows the 48-week virologic response (HIV RNA < 400 and < 50 copies/mL) according to susceptibility and number of genotypic mutations at baseline in 50 evaluable patients enrolled in the Study M98-957 described above. Because this was a select patient population and the sample size was small, the data depicted in **Table 28** do not constitute definitive clinical susceptibility breakpoints. Additional data are needed to determine clinically significant breakpoints for KALETRA.

Table 28 - HIV RNA Response at Week 48 by Baseline KALETRA Susceptibility and by Number of Protease Inhibitor-Associated Mutations[a] – Study M98-957

Lopinavir Susceptibility[b] at Baseline	HIV RNA < 400 copies/mL (%)	HIV 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)
Number of Protease Inhibitor Mutations at Baseline		
Up to 5	21/23 (91)[c]	19/23 (83)
> 5	17/27 (63)	14/27 (52)

a. Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic.
b. Fold change in susceptibility from wild type.
c. Thirteen of the 23 patient isolates contained PI mutations at positions 82, 84, and/or 90.

After 48 weeks of treatment with KALETRA, efavirenz and NRTIs, plasma HIV RNA ≤ 400 copies/mL was observed in 93% (25/27), 73% (11/15), and 25% (2/8) of patients with < 10-fold, 10- to 40-fold, and ≥ 40-fold reduced susceptibility to lopinavir at baseline, respectively.

There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

Genotypic correlates of reduced virologic response in antiretroviral-experienced patients initiating a KALETRA-based combination regimen

Virologic response to KALETRA has been shown to be affected by the presence of 3 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 29** shows the 48-week virologic response (HIV RNA < 400 copies/mL) according to the number of the above PI resistance mutations at baseline in Studies M98-888, M97-765 and M98-957.

Table 29 - Virologic Response (HIV 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 PI mutations at baseline[a]	Study M98-888	Study M97-765	Study M98-957
	Single PI-experienced[b], NNRTI-naïve (n=130)	Single PI-experienced[c], NNRTI-naïve (n=56)	Multiple PI-experienced[d], NNRTI-naïve (n=50)
0 to 2	76/103 (74%)	34/45 (76%)	19/20 (95%)
3 to 5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	N/A	1/4 (25%)

a. 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.

b. 43% indinavir, 42% nelfinavir, 10% ritonavir, 15% saquinavir.

c. 41% indinavir, 38% nelfinavir, 4% ritonavir, 16% saquinavir.

d. 86% indinavir, 54% nelfinavir, 80% ritonavir, 70% saquinavir.

Definitions: NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; N/A=not applicable.

Table 30 shows the 48-week virologic response (HIV-1 RNA < 50 copies/mL) in Study M06-802 according to the number of protease-inhibitor resistance associated mutations listed in **Table 29** present at baseline (see **14 CLINICAL TRIALS**). Based on data derived from a limited number of patients (see **Table 30**), once daily administration of KALETRA is not recommended for adult patients with 3 or more lopinavir resistance-associated substitutions.

Table 30 - Virologic Response (HIV RNA < 50 copies/mL) at Week 48 by Baseline Number of Protease Substitutions Associated with Reduced Response to KALETRA[1]

Number of PI mutations at baseline[a]	Study M06-802 (Treatment-Experienced[b]) KALETRA Once Daily + NRTIs (n=268)	Study M06-802 (Treatment-Experienced[c]) KALETRA Twice Daily + NRTIs (n=264)
0 to 2	167/255 (65%)	154/250 (62%)
3 to 5	4/13 (31%)	8/14 (57%)
6 or more	N/A	N/A

a. 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.

b. 88% NNRTI-experienced, 47% PI-experienced (24% nelfinavir, 19% indinavir, 13% atazanavir).

c. 81% NNRTI-experienced, 46% PI-experienced (20% nelfinavir, 17% indinavir, 13% atazanavir).

Definitions: NRTI = Nucleoside/Nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; N/A = not applicable.

16 NON-CLINICAL TOXICOLOGY

The toxicology of lopinavir has been assessed in mice, rats, dogs and rabbits in studies ranging in duration from a single dose to 9 months of oral administration. The most significant target organ for toxicity in the preclinical toxicity studies has been the liver.

General Toxicology (single and repeat-dose studies)

Acute Toxicity

Lopinavir alone or in combination with ritonavir at a 2:1 ratio has a low order of acute toxicity in rodents by the oral route but is more toxic when administered as an intravenous injection. The acute oral approximate lethal dose (ALD) of lopinavir when given alone was > 2500 mg/kg for rats. Toxic signs were limited to rales and labored/noisy respiration in those rats that received 500 mg/kg or higher. The oral ALD of the lopinavir/ritonavir combination was > 1250/625 mg/kg for both mice and rats. Toxic signs for both species included decreased activity, ataxia, dyspnea, and squinting. In addition, increased salivation was observed in rats.

When administered intravenously, the ALD was > 62.5/31.3 mg/kg for mice and 31.3/15.6 mg/kg for rats. Signs of toxicity for mice included squinting and red or greenish urine. Signs of toxicity for rats included red urine and ataxia. In addition, death was observed in those rats given a dose of 31.3/15.6.mg/kg or higher.

Long-Term Toxicity

Repeated dose toxicity studies in rodent and dogs have identified liver, thyroid, blood, spleen, and kidney as the target organs.

Due to hepatic toxicity (rats) and gastrointestinal toxicity (dogs), the 6-month rat study and the 6- and 9-month dog studies were carried out at systemic exposures lower than exposures of humans at the recommended dose of treatment. Based on the exposures achieved in the long-term toxicity studies in rats and dogs, the clinical relevance of the animal data is unknown. The typical human exposure to lopinavir/ritonavir is approximately 160/10 mcg·h/mL.

Across multiple species (mouse, rat, dog) effects in the liver were fairly similar and most evident following prolonged treatment (3 months or longer). Primary findings were increases in serum liver enzymes (alanine transaminase (ALT) and aspartate transaminase (AST) and sometimes gamma-glutamyl transpeptidase (GGT) or alkaline phosphatase (ALP), cholesterol and histopathological findings of hepatomegaly, single cell necrosis and vacuolar changes primarily in hepatocytes. Less severe toxicity was seen when treatment was initiated in young rats (neonatal at 3 to 4 days old and juvenile at 16 days old) versus adults.

Mild but dose-related hypertrophy of follicular cells in the thyroid gland along with decreased serum thyroxine (T_4) levels and elevated serum thyroid stimulating hormone (TSH) were observed in adult rats that received lopinavir/ritonavir combination for 2 to 26 weeks. Neonatal and juvenile rats appeared to be less sensitive to the thyroid change produced by lopinavir/ritonavir than adult rats. All changes were reversible. No effects on the thyroid gland were observed in any of the mouse (up to 3 months of treatment) or dog studies (up to 9 months of treatment).

Changes in erythrocytic variables included decreases in erythrocyte count, hematocrit, hemoglobin along with an increased incidence and/or severity of anisocytosis (erythrocytes of variable size) and poikilocytosis (erythrocytes with abnormal shapes) observed in rats treated for 3 months or longer.

Changes in kidney were limited to findings in mice and included the presence of microvesicular cytoplasmic vacuolation. Similar vacuolar changes were observed in spleen of treated rats.

Testicular degeneration, generally classified as minimal or mild, was observed in dogs treated for 6 months. Features of the degeneration included loss of germ cells, germ cell degeneration and tubular vacuolization.

Gastrointestinal distress observed shortly after dosing (1 to 2 hours) and consisting of emesis and diarrhea and/or loose stool was dose limiting in dogs.

Carcinogenicity and Mutagenicity

Long-term carcinogenicity studies of up to 2 years duration in mice and rats were conducted for lopinavir/ritonavir at a ratio of 2/1 at maximum tolerated dosages. In mice, dosages of lopinavir/ritonavir of 0/0, 20/10, 60/30, and 120/60 mg/kg/day achieved plasma exposures of up to 2 times (lopinavir) and 5 times (ritonavir) the human therapeutic concentrations. The findings revealed a non-genotoxic, mutagenic induction of hepatocellular adenomas and carcinomas. The relevance to human risk is unknown. In rats, dosages of lopinavir/ritonavir were 0/0, 10/5, 20/10, and 50/25 mg/kg/day and resulted in maximum plasma exposures that were slightly subtherapeutic (0.6 and 0.8 times the therapeutic plasma concentrations for lopinavir and ritonavir, respectively). There was no evidence of carcinogenicity in rats. However, neither lopinavir nor ritonavir, nor lopinavir/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.

Reproductive and Developmental Toxicology

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).

Reproduction

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 (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day 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

post-natal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day 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).

Maternal and Fetal Tissue Distribution

Single oral administration of [^{14}C]-lopinavir in combination with ritonavir to pregnant rats showed that [^{14}C]-lopinavir-derived radioactivity was widely distributed throughout the tissues analyzed, traversed the placental barrier, and was detected in the fetuses of pregnant rats. Maternal and fetal liver had the highest concentration of radioactivity; penetration into the brain was minimal.

Lacteal Excretion

Substantial amounts of radioactivity were observed in the milk following administration of a single oral dose of [^{14}C]-lopinavir (10 mg/kg) given in combination with ritonavir (5 mg/kg). The milk to plasma ratio of radioactivity ranged from 0.084 to 1.53 during 24 hours after dosing. Radioactivity derived from [^{14}C]-lopinavir was detectable in the milk at the first sampling time point, 0.5 hour post-dose. The maximum mean concentration of radioactivity in the milk was 1.93 mcg equivalents [^{14}C]-lopinavir/g at 5 hours post dose. The concentrations declined with time after 5 hours post-dose to a mean value of 0.026 mcg equivalents [^{14}C]-lopinavir/g at 24 hours post-dose.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

KALETRA®

lopinavir / ritonavir tablets

Read this carefully before you start taking **KALETRA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KALETRA**.

If your child is taking **KALETRA**, all of the information in this PATIENT MEDICATION INFORMATION applies to them. As their caregiver, please read this information before they start taking **KALETRA**. Talk to your child's healthcare professional if you need any additional information on their condition and treatment.

Serious Warnings and Precautions

KALETRA can cause **pancreatitis** (inflammation of the pancreas).

Tell your doctor if you develop symptoms, such as:

- abdominal pain
- nausea
- vomiting

These may be signs of **pancreatitis**. Your doctor must decide if these are related to pancreatitis and what to do about them.

What is KALETRA used for?

- the treatment of HIV (Human Immunodeficiency Virus) Infection
- HIV is the virus that causes Acquired Human Immunodeficiency Syndrome (AIDS)
- it is used in adults and children 6 months of age or older
- it is used along other medicines to treat HIV infection

How does KALETRA work?

- KALETRA works by stopping the HIV virus from multiplying. This will help lower the amount of HIV in your body and keep it at a low level.
- KALETRA is not a cure for the HIV infection or AIDS. You can still get infections or other serious illnesses associated with HIV infection or AIDS.

- KALETRA does not reduce the risk of passing HIV to others with sexual contact or blood contamination. You should use appropriate precautions, such as practicing safe sex and not reusing or sharing needles.

What are the ingredients in KALETRA?

Medicinal ingredients: lopinavir and ritonavir

Non-medicinal ingredients: KALETRA 100 / 25 mg tablets also contain colloidal silicon dioxide, copovidone, sodium stearyl fumarate and sorbitan monolaurate. The film-coating ingredients include polyethylene glycol 3350, polyvinyl alcohol, talc, titanium dioxide, and yellow ferric oxide E172.

KALETRA 200 / 50 mg tablets also contain colloidal silicon dioxide, copovidone, sodium stearyl fumarate and sorbitan monolaurate. The film-coating ingredients include colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc, titanium dioxide, and yellow ferric oxide E172.

KALETRA comes in the following dosage forms:

As tablets containing 100 mg of lopinavir and 25 mg of ritonavir.

As tablets containing 200 mg of lopinavir and 50 mg of ritonavir.

Do not use KALETRA if:

- you are allergic to lopinavir, ritonavir or to any of the ingredients in KALETRA.

Do not use KALETRA if you are currently taking any of the following medicines. Taking KALETRA with these can cause serious problems and death:

- alfuzosin, used to treat high blood pressure
- apalutamide, used for prostate cancer
- astemizole and terfenadine, used to relieve allergy symptoms
- carbamazepine, phenytoin and phenobarbital, used as anticonvulsants
- cisapride, used to relieve certain stomach problems
- colchicine, when used in patients with kidney and/or liver problem, used to treat gout
- dronedarone, used to correct heart rhythm
- elbasvir / grazoprevir, used to treat hepatitis C virus infection
- efavirenz, nevirapine and nelfinavir – used to treat HIV
- ergotamine, dihydroergotamine (used to treat headaches), ergonovine, methylergonovine (used after labour and delivery)

- fusidic acid, used as an antibiotic
- lurasidone and pimozide, used to treat mental health problems
- neratinib, used to treat breast cancer
- triazolam and oral midazolam, used to relieve anxiety and trouble sleeping
- ranolazine, used to treat chronic angina (chest pain)
- rifampin, used to treat tuberculosis
- St. John's Wort (*Hypericum perforatum*), an herbal product used to treat depression
- lovastatin, lomitapide or simvastatin, used to lower cholesterol
- PDE5 inhibitors vardenafil, used to treat erectile dysfunction, or sildenafil, used for the treatment of pulmonary arterial hypertension (PAH)
- salmeterol, used for asthma and chronic obstructive pulmonary disease
- venetoclax during the dose initiation and during the ramp-up phase, used to treat chronic lymphocytic leukemia

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KALETRA. Talk about any health conditions or problems you may have, including if you:

- have liver problems.
- are infected with hepatitis B or hepatitis C. If you have liver disease, such as hepatitis B and hepatitis C, taking KALETRA may worsen your liver disease.
- have diabetes or symptoms, such as frequent urination and/or increase in thirst.
- have hemophilia, since KALETRA can increase bleeding in these patients.
- have heart disease or a heart condition, including conditions of Congenital Long QT Syndrome.
- have low potassium levels in your blood.
- have been told you have high triglyceride levels in your blood.
- have had a condition called pancreatitis in the past.

Other warnings you should know about:

Pregnancy

Tell your doctor if you are pregnant or planning to become pregnant. It is not known if KALETRA can harm your unborn baby. Tell your doctor if you become pregnant while you are taking KALETRA.

Pregnancy Registry

There is a pregnancy registry for women who take antiretroviral medicines while they are pregnant. The purpose of this registry is to collect information about the health of you and your baby. If you do become pregnant while taking KALETRA, talk to your doctor about taking part in this registry.

Breastfeeding

You should not breastfeed if you are taking KALETRA. You should also not breastfeed a baby if you are infected with HIV. This is because you can pass HIV to your baby.

Severe Liver Problems

Severe liver problems, including deaths, have been reported in those using KALETRA. This has often occurred in those with advanced HIV disease, other liver disease or those taking many medications. There is no proven link to KALETRA use. Symptoms of serious liver problems include yellow skin and whites of eyes, nausea, tiredness, loss of appetite, fever, skin rash, pain in the upper abdomen, pale stools and dark-coloured urine. Talk to your doctor if you get any of these symptoms.

Contraception

If you are taking oral contraceptives ("the pill") or the contraceptive patch (i.e., ethinyl estradiol) to prevent pregnancy, you should use a different type of contraception since KALETRA may reduce the effectiveness of oral or patch contraceptives.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following medicines should only be used together with KALETRA if advised by your physician.

The following may interact with KALETRA:

- medicines used to treat erectile dysfunction, such as tadalafil
- medicines used to treat pulmonary arterial hypertension, such as bosentan or tadalafil
- medicines used to lower blood cholesterol, such as rosuvastatin and atorvastatin
- some medicines affecting the immune system, such as cyclosporin, sirolimus and tacrolimus
- some medicines used to treat seasonal allergies and ear and eye infections, such as dexamethasone, fluticasone propionate and triamcinolone
- medicines used to treat asthma, such as budesonide

- contraceptives used to prevent pregnancy (e.g., ethinyl estradiol)
- medicines used to treat AIDS and related infections, such as amprenavir, fosamprenavir, indinavir, saquinavir, didanosine, tenofovir, maraviroc, rifabutin, etravirine, rilpivirine, tipranavir when used with low-dose ritonavir
- medicines used to treat HCV and related infections, such as telaprevir, boceprevir, glecaprevir / pibrentasvir, sofosbuvir / velpatasvir / voxilaprevir, simeprevir and ombitasvir / paritaprevir / ritonavir with or without dasabuvir
- medicines used to treat depression, such as trazodone and bupropion
- certain heart medicines, such as calcium channel antagonists including felodipine, nifedipine and nicardipine
- medicines used to correct heart rhythm, such as amiodarone, flecainide, bepridil, systemic lidocaine, propafenone hydrochloride, quinidine and digoxin
- antifungals, such as ketoconazole, itraconazole and voriconazole
- morphine-like medicines used to treat severe pain, such as methadone
- anticonvulsants, such as lamotrigine and valproate
- anticoagulants, such as warfarin or rivaroxaban
- certain antibiotics, such as clarithromycin
- medicines used to treat cancer, such as abemaciclib, dasatinib, encorafenib, ibrutinib, nilotinib, vincristine and vinblastine, as KALETRA may increase the concentrations of these drugs and increase adverse effects
- medicines used for low blood platelet count, such as fostamatinib
- fentanyl, used to treat pain in all forms, as this interaction may reduce breathing
- quetiapine, used to treat schizophrenia, bipolar disorder and major depressive disorder
- medicines used to treat pain associated with endometriosis, such as elagolix

How to take KALETRA:

- Take KALETRA exactly as your doctor tells you to.
- Do not change your dose or stop taking KALETRA without talking to your doctor.
- You must stay under your doctor's care when taking KALETRA.
- Swallow the KALETRA tablets whole. Do not chew, break or crush tablets.

- You may take KALETRA tablets with or without food.

Usual dose:

- Your doctor will tell you how much KALETRA you should take and when you should take it.
- KALETRA is always taken along with other medicines used to treat HIV Infection.
- The usual dose for adults is two 200 / 50 mg tablets twice a day.
- The doctor might prescribe KALETRA as four 200 / 50 mg tablets once a day for certain patients.
- The usual dose for children 6 months to 18 years of age will be based on a child's height and weight. The child's doctor will decide what dose a child should receive.
- KALETRA is always given twice a day for children.

Overdose:

If you think you have taken too much KALETRA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you missed a dose of this medication, it should be taken as soon as you remember. If it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take 2 doses at the same time.

What are possible side effects from using KALETRA?

These are not all the possible side effects you may feel when taking KALETRA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Diarrhea
- Feeling weak or tired
- Headache
- Rash
- Some patients have large increases in triglycerides and cholesterol (forms of fat that are found in your blood).

Changes to your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

Autoimmune disorders (when the immune system attacks healthy body tissue) may also occur after you start taking medicines for HIV infection. Examples of this include: **Grave's disease** (which affects the thyroid gland), **Guillain-Barré syndrome** (which affects the nervous system), **polymyositis** (which affects the muscles), or **autoimmune hepatitis** (which affects the liver). Autoimmune disorders may occur at any time, even many months after the start of treatment.

If you are experiencing new symptoms, call your doctor immediately, for example:

- high temperature (fever), redness, rash or swelling
- fatigue
- joint or muscle pain
- numbness, tingling, or weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations (chest pain) or rapid heart rate
- yellowing of the skin or eyes
- anxiety and irritability accompanied by tremor of your hands or fingers
- muscle weakness in your hips, thighs, shoulders, upper arms, and neck

Your doctor may monitor blood levels of fats (lipids), cholesterol and glucose before and during KALETRA treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Neuropathy and peripheral neuropathy: tingling feeling in hands, feet and around lips	✓		
UNCOMMON			
Chest pain		✓	
Pancreatitis (inflammation of the pancreas): abdominal pain, nausea, and vomiting		✓	
Severe liver problems: yellow skin and whites of eyes, nausea, tiredness, loss of appetite, fever, skin rash, pain in the upper		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
abdomen, pale stools, dark-coloured urine			
Diabetes and high blood sugar: increased thirst, frequent urination		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15 and 30°C. It is recommended that the product be stored and dispensed in the original container.

Do not use after the expiry date on the package.

Keep out of the sight and reach of children.

If you want more information about KALETRA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.abbvie.ca), or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

KALETRA®

lopinavir / ritonavir oral solution

Read this carefully before you start taking **KALETRA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KALETRA**.

If your child is taking **KALETRA**, all of the information in this PATIENT MEDICATION INFORMATION applies to them. As their caregiver, please read this information before they start taking **KALETRA**. Talk to your child's healthcare professional if you need any additional information on their condition and treatment.

Serious Warnings and Precautions

KALETRA can cause **pancreatitis** (inflammation of the pancreas).

Tell your doctor if you develop symptoms, such as:

- abdominal pain
- nausea
- vomiting

These may be signs of **pancreatitis**. Your doctor must decide if these are related to pancreatitis and what to do about them.

What is KALETRA used for?

- the treatment of HIV (Human Immunodeficiency Virus) Infection
- HIV is the virus that causes Acquired Human Immunodeficiency Syndrome (AIDS)
- it is used in adults and children 6 months of age or older
- it is used along other medicines to treat HIV infection

How does KALETRA work?

- KALETRA works by stopping the HIV virus from multiplying. This will help lower the amount of HIV in your body and keep it at a low level.
- KALETRA is not a cure for the HIV infection or AIDS. You can still get infections or other serious illnesses associated with HIV infection or AIDS.

- KALETRA does not reduce the risk of passing HIV to others with sexual contact or blood contamination. You should use appropriate precautions, such as practicing safe sex and not reusing or sharing needles.

What are the ingredients in KALETRA?

Medicinal ingredients: lopinavir and ritonavir

Non-medicinal ingredients: KALETRA oral solution also contains acesulfame potassium, alcohol, artificial cotton candy flavour, citric acid, glycerine, high fructose corn syrup, Magnasweet-110 flavour, menthol, natural and artificial vanilla flavour, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

KALETRA comes in the following dosage forms:

As an oral solution. Each mL of KALETRA contains 80 mg of lopinavir and 20 mg of ritonavir.

Do not use KALETRA if:

- you are allergic to lopinavir, ritonavir or to any of the ingredients in KALETRA.

Do not use KALETRA if you are currently taking any of the following medicines. Taking KALETRA with these can cause serious problems and death:

- alfuzosin, used to treat high blood pressure
- apalutamide, used for prostate cancer
- astemizole and terfenadine, used to relieve allergy symptoms
- carbamazepine, phenytoin and phenobarbital, used as anticonvulsants
- cisapride, used to relieve certain stomach problems
- colchicine, when used in patients with kidney and/or liver problem, used to treat gout
- dronedarone, used to correct heart rhythm
- elbasvir / grazoprevir, used to treat hepatitis C virus infection
- efavirenz, nevirapine and nelfinavir – used to treat HIV
- ergotamine, dihydroergotamine (used to treat headaches), ergonovine, methylergonovine (used after labour and delivery)
- fusidic acid, used as an antibiotic
- lurasidone and pimozide, used to treat mental health problems
- neratinib, used to treat breast cancer
- triazolam and oral midazolam, used to relieve anxiety and trouble sleeping
- ranolazine, used to treat chronic angina (chest pain)

- rifampin, used to treat tuberculosis
- St. John's Wort (*Hypericum perforatum*), an herbal product used to treat depression
- lovastatin, lomitapide or simvastatin, used to lower cholesterol
- PDE5 inhibitors vardenafil, used to treat erectile dysfunction, or sildenafil, used for the treatment of pulmonary arterial hypertension (PAH)
- salmeterol, used for asthma and chronic obstructive pulmonary disease
- venetoclax at the dose initiation and during the ramp-up phase, used to treat chronic lymphocytic leukemia

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KALETRA. Talk about any health conditions or problems you may have, including if you:

- have liver problems.
- are infected with hepatitis B or hepatitis C. If you have liver disease, such as hepatitis B and hepatitis C, taking KALETRA may worsen your liver disease.
- have diabetes or symptoms, such as frequent urination and/or increase in thirst.
- have hemophilia, since KALETRA can increase bleeding in these patients.
- have heart disease or a heart condition, including conditions of Congenital Long QT Syndrome.
- have low potassium levels in your blood.
- have hereditary fructose intolerance since the KALETRA oral solution contains fructose.
- have kidney problems or inability to metabolize propylene glycol (such as in patients of Asian origin) as the KALETRA oral solution contains propylene glycol.
- suffer from alcoholism, epilepsy or brain injury, as the KALETRA oral solution contains alcohol.
- have been told you have high triglyceride levels in your blood.
- have had a condition called pancreatitis in the past.

Other warnings you should know about:

Pregnancy

Tell your doctor if you are pregnant or planning to become pregnant. It is not known if KALETRA can harm your unborn baby. Tell your doctor if you become pregnant while you are taking KALETRA. The KALETRA oral solution should not be used during pregnancy since it contains alcohol and propylene glycol.

Pregnancy Registry

There is a pregnancy registry for women who take antiretroviral medicines while they are pregnant. The purpose of this registry is to collect information about the health of you and your baby. If you do become pregnant while taking KALETRA, talk to your doctor about taking part in this registry.

Breastfeeding

You should not breastfeed if you are taking KALETRA. You should also not breastfeed a baby if you are infected with HIV. This is because you can pass HIV to your baby.

Severe Liver Problems

Severe liver problems, including deaths, have been reported in those using KALETRA. This has often occurred in those with advanced HIV disease, other liver disease or those taking many medications. There is no proven link to KALETRA use. Symptoms of serious liver problems include yellow skin and whites of eyes, nausea, tiredness, loss of appetite, fever, skin rash, pain in the upper abdomen, pale stools, and dark-coloured urine. Talk to your doctor if you get any of these symptoms.

Contraception

If you are taking oral contraceptives ("the pill") or the contraceptive patch (i.e., ethinyl estradiol) to prevent pregnancy, you should use a different type of contraception since KALETRA may reduce the effectiveness of oral or patch contraceptives.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following medicines should only be used together with KALETRA if advised by your physician.

The following may interact with KALETRA:

- medicines used to treat erectile dysfunction, such as tadalafil
- medicines used to treat pulmonary arterial hypertension, such as bosentan or tadalafil
- medicines used to lower blood cholesterol, such as rosuvastatin and atorvastatin
- some medicines affecting the immune system, such as cyclosporin, sirolimus and tacrolimus
- some medicines used to treat seasonal allergies and ear and eye infections, such as dexamethasone, fluticasone propionate and triamcinolone
- medicines used to treat asthma, such as budesonide
- contraceptives used to prevent pregnancy (e.g., ethinyl estradiol)
- medicines used to treat AIDS and related infections, such as amprenavir, fosamprenavir, indinavir, saquinavir, didanosine, tenofovir, maraviroc, rifabutin, etravirine, rilpivirine, tipranavir when used with low-dose ritonavir

- medicines used to treat HCV and related infections, such as telaprevir, boceprevir, glecaprevir / pibrentasvir, sofosbuvir / velpatasvir / voxilaprevir, simeprevir and ombitasvir / paritaprevir / ritonavir with or without dasabuvir
- medicines used to treat depression, such as trazodone and bupropion
- certain heart medicines, such as calcium channel antagonists including felodipine, nifedipine and nicardipine
- medicines used to correct heart rhythm, such as amiodarone, flecainide, bepridil, systemic lidocaine, propafenone hydrochloride, quinidine, and digoxin
- antifungals, such as ketoconazole, itraconazole and voriconazole
- morphine-like medicines used to treat severe pain, such as methadone
- anticonvulsants, such as lamotrigine and valproate
- anticoagulants, such as warfarin or rivaroxaban
- certain antibiotics, such as clarithromycin
- medicines used to treat cancer, such as abemaciclib, dasatinib, encorafenib, ibrutinib, nilotinib, vincristine and vinblastine, as KALETRA may increase the concentrations of these drugs and increase adverse effects
- medicines used for low blood platelet count, such as fostamatinib
- fentanyl, used to treat pain in all forms, as this interaction may reduce breathing
- quetiapine, used to treat schizophrenia, bipolar disorder, and major depressive disorder
- medicines used to treat pain associated with endometriosis, such as elagolix

How to take KALETRA:

- Take KALETRA exactly as your doctor tells you to.
- Do not change your dose or stop taking KALETRA without talking to your doctor.
- You must stay under your doctor's care when taking KALETRA.

Usual dose:

- Your doctor will tell you how much KALETRA you should take and when you should take it.
- KALETRA is always taken along with other medicines used to treat HIV infection.
- The usual dose for adults is 5 mL of the oral solution twice a day.
- It may also be given as 10 mL of the oral solution once a day in some patients.
- For children aged 6 months to 18 years, the dose they are given will be based on their height and weight.
- KALETRA is always given twice a day for children.

- You must take the KALETRA oral solution with food.

Overdose:

If you think you have taken too much KALETRA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

KALETRA oral solution contains 42% alcohol and 15% propylene glycol and accidental ingestion could be toxic and could kill a young child. Keep KALETRA and all other medicines out of the reach and sight of children.

Missed dose:

If you missed a dose of this medication, it should be taken as soon as you remember. If it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take 2 doses at the same time.

What are possible side effects from using KALETRA?

These are not all the possible side effects you may feel when taking KALETRA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Diarrhea
- Feeling weak or tired
- Headache
- Rash
- Some patients have large increases in triglycerides and cholesterol (forms of fat that are found in your blood).

Changes to your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

Autoimmune disorders (when the immune system attacks healthy body tissue) may also occur after you start taking medicines for HIV infection. Examples of this include: **Grave's disease** (which affects the thyroid gland), **Guillain-Barré syndrome** (which affects the nervous system), **polymyositis** (which affects the muscles), or **autoimmune hepatitis** (which affects the liver). Autoimmune disorders may occur at any time, even many months after the start of treatment.

If you are experiencing new symptoms, call your doctor immediately, for example:

- high temperature (fever), redness, rash or swelling
- fatigue
- joint or muscle pain
- numbness, tingling, or weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations (chest pain) or rapid heart rate
- yellowing of the skin or eyes
- anxiety and irritability accompanied by tremor of your hands or fingers
- muscle weakness in your hips, thighs, shoulders, upper arms, and neck

Your doctor may monitor blood levels of fats (lipids), cholesterol and glucose before and during KALETRA treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Neuropathy and peripheral neuropathy: tingling feeling in hands, feet and around lips	✓		
UNCOMMON			
Chest pain		✓	
Pancreatitis (inflammation of the pancreas): abdominal pain, nausea and vomiting		✓	
Severe liver problems: yellow skin and whites of eyes, nausea, tiredness, loss of appetite, fever, skin rash, pain in the upper abdomen, pale stools, dark-coloured urine		✓	
Diabetes and high blood sugar: increased thirst, frequent urination		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2 and 8°C in a refrigerator. If you keep KALETRA outside of a refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). Avoid exposure to excessive heat. Keep cap tightly closed.

Keep KALETRA in the original package. Do not transfer to any other container.

Do not use after the expiry date on the package.

Keep out of the sight and reach of children.

If you want more information about KALETRA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.abbvie.ca), or by calling 1-888-704-8271.

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