PRODUCT MONOGRAPH

PR KALETRA®
lopinavir/ritonavir
film-coated tablets (100 mg/25 mg, 200 mg/50 mg)

PR KALETRA®
lopinavir/ritonavir
soft gel capsules (133.3 mg/33.3 mg)

PR KALETRA®
lopinavir/ritonavir
oral solution (80/20 mg/mL)

Human Immunodeficiency Virus (HIV) Protease Inhibitor

Date of Preparation:
March 9, 2001

Date of Previous Revision:
June 10, 2008

Date of Revision:

November 5, 2009

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Submission Control No: 131811

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PrKALETRA®

lopinavir/ritonavir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
oral	film-coated tablets / 100 mg/25 mg, 200 mg/50 mg	sorbitan monolaurate
	soft gel capsules / 133.3 mg/33.3 mg	polyoxyl 35 castor oil and propylene glycol
	oral solution / 80/20 mg/mL	alcohol, fructose, polyoxyl 40 hydrogenated castor oil and propylene glycol
		*For a complete listing of non-medicinal ingredients, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

DESCRIPTION

KALETRA® (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the Human Immunodeficiency Virus (HIV) protease. As co-formulated in KALETRA®, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

INDICATIONS AND CLINICAL USE

KALETRA® (lopinavir/ritonavir) is indicated in combination with other antiretroviral agents when therapy is warranted for:

- treatment of HIV-1 infection

This indication is based on analyses of plasma HIV RNA levels and CD_4 cell counts in controlled KALETRA® studies of 48 weeks duration, and in smaller uncontrolled KALETRA® dose-ranging studies of 144 to 360 weeks duration. At present, there are no results from controlled trials evaluating the effect of KALETRA® on clinical progression of HIV disease. A limited number of patients between 6 months and 2 years of age have been studied. No data are available on patients less than 6 months of age.

Once daily administration of KALETRA® is not recommended in therapy-experienced patients.

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.

Pediatrics (6 months to 12 years of age):

The safety and pharmacokinetic profiles of KALETRA® in pediatric patients below the age of 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of KALETRA® in pediatric patients in clinical trials is ongoing. See (**CLINICAL TRIALS**, **Pediatric Use**). KALETRA® should not be administered once daily to pediatric patients less than 18 years of age.

CONTRAINDICATIONS

- KALETRA® (lopinavir/ritonavir) is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir. For a complete listing, see the **DOSAGE FORMS, 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**.

Table 1. Drugs that are Contraindicated with KALETRA®

Drug Class	Drugs Within Class That Are Contraindicated with KALETRA®	Clinical Comment
Antihistamines	astemizole[1], terfenadine[1]	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial	rifampin	CONTRAINDICATED due to potential loss of virologic response and possible resistance to KALETRA® or to the class of protease inhibitors or other co-administered antiretroviral agents. See (**DETAILED PHARMACOLOGY, Pharmacokinetics**, **Effect of Co-Administered Drugs on Lopinavir**, **Table 30**, Rifampin) for further details.
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to 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[1]	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	CONTRAINDICATED due to potential loss of virologic response and possible resistance to KALETRA® or to the class of protease inhibitors. See also (**DRUG INTERACTIONS**, **Drug-Herb Interactions**).
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	CONTRAINDICATED due to potential for serious reactions such as risk of myopathy including rhabdomyolysis. See also (**WARNINGS AND PRECAUTIONS**) and (**DRUG INTERACTIONS, Serious Drug Interactions**).
Long Acting Beta-Adrenoceptor Agonist	Salmeterol	CONTRAINDICATED due to the potential increased risk of cardiovascular adverse events associated with salmeterol.
Neuroleptic	Pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
PDE5 Inhibitors	Sildenafil (Revatio®; only when used for the treatment of	CONTRAINDICATED due to potential increase in PDE5 inhibitor associated

Drug Class	Drugs Within Class That Are Contraindicated with KALETRA®	Clinical Comment
	pulmonary arterial hypertension [PAH]), vardenafil	adverse reactions including hypotension, syncope, visual changes and prolonged erection. See **DRUG INTERACTIONS, Drug-Drug Interactions, Table 7** for administration of sildenafil in patients with erectile dysfunction.
Sedatives/Hypnotics	midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

1: Product not marketed in Canada.

WARNINGS AND PRECAUTIONS

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 (**WARNINGS AND PRECAUTIONS**, **hepatic/biliary/pancreatic**).

General

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®. Thus, co-administration of KALETRA® with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring. Additionally, KALETRA® induces glucuronidation. See (**CONTRAINDICATIONS**, **Table 1**) and (**DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Table 7**) and (**ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics, Table 31**).

The presence of fructose in KALETRA® oral solution may be unsuitable in Hereditary Fructose Intolerance. See (**DOSAGE FORMS, COMPOSITION AND PACKAGING**).

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 (**DOSAGE FORMS, 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).

Carcinogenesis and Mutagenesis

For a brief discussion of pre-clinical animal data, see (**TOXICOLOGY**, **Mutagenicity and Carcinogenicity**).

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 (**ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics**, **Effect on the Electrocardiogram**).

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.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-1 infected patients receiving protease inhibitor (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.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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 (**ACTION AND CLINICAL PHARMACOLOGY**, **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. Increased aspartate transaminase (AST) and alanine transaminase (ALT) monitoring should be considered in these patients, especially during the first several months of KALETRA® treatment.

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 (**WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**, **Lipid Elevations**). 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

Immune reconstitution 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 jiroveci pneumonia* (PCP), and tuberculosis (TB)], which may necessitate further evaluation and treatment.

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 (**ACTION AND CLINICAL PHARMACOLOGY**, **Resistance** and **Cross-resistance**).

Special Populations

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. KALETRA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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 (**TOXICOLOGY, Reproduction and Teratology, Reproduction**).

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.

Nursing Women

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®**.

Pediatrics (6 months to 12 years of age)

For a brief discussion, see **INDICATIONS AND CLINICAL USE**.

Geriatrics (≥ 65 years of age)

For a brief discussion, see **INDICATIONS AND CLINICAL USE**.

Monitoring and Laboratory Tests

Lipid Elevations

Treatment with KALETRA® has resulted in large increases in the concentration of total cholesterol and triglycerides. See (**ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**, **Table 4** and **Table 5**). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA® therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **Table 7** for additional information on potential drug interactions with KALETRA® and HMG-CoA reductase inhibitors.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

Treatment-Emergent Adverse Events

Adults

KALETRA® (lopinavir/ritonavir) has been studied in 1555 patients as combination therapy in Phase 1/2 and Phase 3 clinical trials. The most common adverse event associated with KALETRA® therapy was diarrhea, which was generally of mild to moderate severity, nausea, abdominal pain, asthenia, vomiting, headache, and dyspepsia. The incidence of diarrhea was greater for KALETRA® capsule once daily compared to KALETRA® capsule twice daily in Study III (see **Table 2**).

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 2**. For other information regarding observed or potentially serious adverse events, see **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 3**. 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 XI.

Pediatrics

KALETRA® has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Taste aversion (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 VI. A total of eight subjects experienced adverse events of moderate to severe intensity and of possible, probable, or unknown relationship to KALETRA®. The adverse events meeting these criteria and reported for the eight subjects 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 taste perversion. Rash was the only event of those listed that occurred in two or more subjects (n=3).

Table 2. Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

	Study I (48 Weeks)		Study III (48 Weeks)		Study II (360 Weeks)	Study XI (48 Weeks)	
	KALETRA® capsules 400/100 mg b.i.d. + d4T + 3TC (N=326)	nelfinavir 750 mg t.i.d. + d4T + 3TC (N=327)	KALETRA® capsules 800/200 mg daily + TDF + FTC (N=115)	KALETRA® capsules 400/100 mg b.i.d. + TDF + FTC (N=75)	KALETRA® capsules b.i.d.[2] + d4T + 3TC (N=100)	KALETRA® tablets[3] 800/200mg daily + TDF + FTC (N=333)	KALETRA® tablets[3] 400/100mg b.i.d. + TDF + FTC (N=331)
Endocrine Disorders							
Hypogonadism	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%
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%
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%	2%
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%

	Study I (48 Weeks)		Study III (48 Weeks)		Study II (360 Weeks)	Study XI (48 Weeks)	
	KALETRA® capsules 400/100 mg b.i.d. + d4T + 3TC (N=326)	**nelfinavir 750 mg t.i.d. + d4T + 3TC (N=327)**	**KALETRA® capsules 800/200 mg daily + TDF + FTC (N=115)**	**KALETRA® capsules 400/100 mg b.i.d. + TDF + FTC (N=75)**	**KALETRA® capsules b.i.d.[2] + d4T + 3TC (N=100)**	**KALETRA® tablets[3] 800/200mg daily + TDF + FTC (N=333)**	**KALETRA® tablets[3] 400/100mg b.i.d. + TDF + FTC (N=331)**
Libido decreased	< 1%	< 1%	0%	1%	2%	1%	< 1%
Reproductive System and Breast Disorders							
Amenorrhea	0%	0%	5%	0%	0%	0%	0%
Skin and Subcutaneous Tissue Disorders							
Rash	1%	2%	1%	0%	5%	< 1%	1%
Vascular Disorders							
Vasodilatation	0%	0%	0%	0%	3%	0%	0%

1: Includes adverse events of possible, probable or unknown relationship to study drug.

2: 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 b.i.d. [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.

3: 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 3. Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in > 2% of Adult Protease Inhibitor-Experienced Patients

	Study IV (48 Weeks)		Study VII[2] and Study V[3] (84 to 144 Weeks)
	KALETRA® capsules 400/100 mg b.i.d. + NVP + NRTIs (N=148)	Investigator-selected PI(s) + NVP + NRTIs (N=140)	KALETRA® capsules b.i.d. + NNRTI + NRTIs (N=127)
Gastrointestinal Disorders			
Diarrhea	7%	9%	23%
Nausea	7%	16%	5%
Vomiting	4%	12%	2%
Abdominal Pain	2%	2%	4%
Dyspepsia	1%	1%	2%
Flatulence	1%	2%	2%
Dysphagia	2%	1%	0%
General Disorders and Administration Site Conditions			
Asthenia	3%	6%	9%
Pyrexia	2%	1%	2%
Chills	2%	0%	0%
Investigations			
Weight decreased	0%	1%	3%
Metabolism and Nutrition Disorders			
Anorexia	1%	3%	0%
Musculoskeletal and Connective Tissue Disorders			
Myalgia	1%	1%	2%
Nervous System Disorders			
Headache	2%	3%	2%
Paresthesia	1%	0%	2%
Psychiatric Disorders			
Depression	1%	2%	2%
Insomnia	0%	2%	2%
Skin and Subcutaneous Tissue Disorders			
Rash	2%	1%	2%
Vascular Disorders			
Hypertention	0%	0%	2%

	Study IV (48 Weeks)		Study VII[2] and Study V[3] (84 to 144 Weeks)
	KALETRA® capsules 400/100 mg b.i.d. + NVP + NRTIs	**Investigator-selected PI(s) + NVP + NRTIs**	**KALETRA® capsules b.i.d. + NNRTI + NRTIs**
	(N=148)	**(N=140)**	**(N=127)**

1: Includes adverse events of possible, probable or unknown relationship to study drug.

2: 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.

3: 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.

2, 3: Average of Studies VII and V; both studies have subjects dosed with KALETRA® + NNRTI + NRTIs.

Definitions: b.i.d. = twice daily; NNRTI = non-nucleoside reverse transciptase inhibitor; NRTI = nucleoside reverse transciptase inhibitor; NVP = nevirapine; PI = protease inhibitor.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving KALETRA® in all Phase 2/3 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:	Anemia, leucopenia, lymphadenopathy, and splenomegaly.
Cardiac Disorders:	Atrial fibrillation, atrioventricular block, hypertension, myocardial infarction, and palpitations.
Ear and Labyrinth Disorders:	Hyperacusis, tinnitus, and vertigo.
Endocrine Disorders:	Avitaminosis, Cushing's syndrome, and hypothyroidism.
Eye Disorders:	Eye disorder, and visual disturbance.
Gastrointestinal Disorders:	Abdominal pain upper, constipation, dry mouth, enteritis, enterocolitis, enterocolitis hemorrhagic, eructation, esophagitis, fecal incontinence, gastric disorder, gastritis, gastroesophageal reflux disease, hemorrhoids, mouth ulceration, pancreatitis, periodontitis, stomach discomfort, and stomatitis.
General Disorders and Administration Site Conditions:	Chest pain, chest pain substernal, cyst, drug interaction, edema, edema peripheral, face edema, fatigue, hypertrophy, lipodystrophy, and malaise.
Hepatobiliary Disorders:	Cholangitis, cholecystitis, cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly, jaundice, and liver tenderness.
Immune System Disorders:	Allergic reaction, drug hypersensitivity, hypersensitivity, and immune reconstitution syndrome.
Infection and Infestations:	Bacterial infection, cellulitis, folliculitis, furuncle, gastroenteritis, influenza, otitis media, perineal abscess, pharyngitis, rhinitis, sialoadenitis, sinusitis, and viral infections.
Investigations:	Drug level increased, glucose tolerance decreased, and weight increased.
Metabolism and Nutrition Disorders:	Decreased appetite, dehydration, diabetes mellitus, dislipidaemia, hypovitaminosis, increased appetite, lactic acidosis, lipomatosis, and obesity.
Musculoskeletal and Connective Tissue Disorders:	Arthralgia, arthropathy, back pain, muscular weakness, osteoarthritis, osteonecrosis, and pain in extremity.

Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps):	Benign neoplasm of skin, lipoma, and neoplasm.
Nervous System Disorders:	Ageusia, amnesia, ataxia, cerebral infarction, convulsion, dizziness, dysgeusia, dyskinesia, encephalopathy, extrapyramidal disorder, facial palsy, hypertonia, migraine, neuropathy, neuropathy peripheral, somnolence, and tremor.
Psychiatric Disorders:	Abnormal dreams, affect lability, agitation, anxiety, apathy, confusional state, nervousness, and thinking abnormal.
Renal and Urinary Disorders:	Nephritis, nephrolithiasis, renal disorder, and urine abnormality.
Reproductive System and Breast Disorders:	Breast enlargement, ejaculation disorder, erectile dysfunction, and gynecomastia.
Respiratory, Thoracic and Mediastinal Disorders:	Asthma, cough, dyspnea, and pulmonary edema.
Skin and Subcutaneous Tissue Disorders:	Acne, alopecia, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, dry skin, eczema, hyperhidrosis, idiopathic capillaritis, nail disorder, pruritis, rash generalized, rash maculo-papular, seborrhea, skin discoloration, skin hypertrophy, skin striae, skin ulcer, and swelling face.
Vascular Disorders:	Deep vein thrombophlebitis, deep vein thrombosis, orthostatic hypotension, thrombophlebitis, varicose vein, and vasculitis.

Abnormal Hematologic and Clinical Chemistry Findings

The percentages of adult antiretroviral-naïve and PI-experienced patients treated with combination therapy including KALETRA® with Grade 3-4 laboratory abnormalities are presented in **Table 4** and **Table 5**.

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

		Study I (48 Weeks)		Study III (48 Weeks)		Study II (360 Weeks)	Study XI (48 Weeks)	
Variable	**Limit**	**KALETRA® capsules 400/100 mg b.i.d. + d4T + 3TC (N=326)**	**Nelfinavir 750 mg t.i.d. + d4T + 3TC (N=327)**	**KALETRA® capsules 800/200 mg daily + TDF + FTC (N=115)**	**KALETRA® capsules 400/100 mg b.i.d. + TDF + FTC (N=75)**	**KALETRA® capsules b.i.d.[1] + d4T + 3TC (N=100)**	**KALETRA® tablets[2] 800/200mg daily + TDF + FTC (N=333)**	**KALETRA® tablets[2] 400/100mg b.i.d. + TDF + FTC (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%
SGOT/AST [3]	>5 x ULN	2%	4%	5%	3%	10%	1%	2%
SGPT/ALT [3]	>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	<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%

1: 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 b.i.d. [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.

2: 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.

3: Criterion for Study XI was >5 x ULN (AST/ALT)

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

Variable	Limit	Study IV (48 Weeks)		Studies VII [1] and V [2] (84 to 144 Weeks)
		KALETRA® capsules 400/100 mg b.i.d. + NVP + NRTIs (N=148)	Investigator-selected PI(s) + NVP + NRTIs (N=140)	KALETRA® capsules b.i.d. + NNRTI + NRTIs (N=127)
Chemistry	**High**			
Glucose	> 13.8 mmol/L	1%	2%	5%
Uric Acid	> 0.71 mmol/L	0%	1%	1%
Total Bilirubin	> 59.5 micromol/L	1%	3%	1%
SGOT/AST	> 5 x ULN	5%	11%	8%
SGPT/ALT	> 5 x ULN	6%	13%	10%
GGT	> 5 x ULN	N/A	N/A	29%
Total Cholesterol	> 7.77 mmol/L	20%	21%	39%
Triglycerides	> 8.25 mmol/L	25%	21%	36%
Amylase	> 2 x ULN	4%	8%	8%
Chemistry	**Low**			
Inorganic Phosphorous	< 0.48 mmol/L	1%	0%	2%
Hematology	**Low**			
Neutrophils	0.75 x 10^9/L	1%	2%	4%

1: 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.

2: 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.

Definitions: b.i.d. = twice daily; NRTI = nucleoside reverse transciptase inhibitor; NNRTI = non-nucleoside reverse transciptase 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.

The percentages of pediatric patients treated with combination therapy including KALETRA® with Grade 3-4 laboratory abnormalities are presented in **Table 6**.

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

Variable	Limit	KALETRA® oral solution b.i.d.[1] + 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%

1: 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.

Post-Market Adverse Drug Reactions

Hepatitis has been reported in patients on KALETRA® therapy.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia has been reported during post-marketing surveillance in HIV-infected patients receiving PI therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events.

Stevens Johnson Syndrome and erythema multiforme have been reported.

Bradyarrhythmia has been reported.

DRUG INTERACTIONS

Serious Drug Interactions

- **Antihistamines** (astemizole*, terfenadine*): **CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
- **Antimycobacterial** (rifampin): **CONTRAINDICATED** due to potential loss of virologic response and possible resistance to KALETRA® (lopinavir/ritonavir) or to the class of protease inhibitors or other co-administered antiretroviral agents. KALETRA® should not be co-administered with rifampin.
- **Ergot Derivatives** (dihydroergotamine, ergonovine, ergotamine, methylergonovine): **CONTRAINDICATED** due to 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.
- **GI (Gastrointestinal) Motility Agent** (cisapride*): **CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
- **Herbal Products** (St. John's Wort): **CONTRAINDICATED** due to potential loss of virologic response and possible resistance to KALETRA® or to the class of protease inhibitors.
- **HMG-CoA Reductase Inhibitors** (lovastatin, simvastatin): **CONTRAINDICATED** due to potential for serious reactions such as risk of myopathy including rhabdomyolysis. KALETRA® should not be co-administered with these drugs.
- **Long Acting Beta-Adrenoceptor Agonist** (salmeterol): **CONTRAINDICATED** due to the potential increased risk of cardiovascular adverse events associated with salmeterol.
- **Neuroleptic** (pimozide): **CONTRAINDICATED** due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
- **PDE5 Inhibitors** (sildenafil [only when used for the treatment of pulmonary arterial hypertension], vardenafil): **CONTRAINDICATED** due to potential increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection.

Serious Drug Interactions (Continued)

- **Sedatives/Hypnotics** (midazolam, triazolam): CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

* Product not marketed in Canada.

Overview

No drug interaction studies were performed with the once daily regimen of KALETRA® (lopinavir/ritonavir).

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 (**DRUG INTERACTIONS, Drug-Drug Interactions**, **Table** 7). 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 (**DRUG INTERACTIONS, Drug-Drug Interactions**, **Table 7**). Co-administration of KALETRA® and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with KALETRA® and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. **Table** 7 presents established and other potentially significant drug interactions with lopinavir. The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased). For information regarding clinical recommendations, see (**DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Table 7**).

Possible Dose Adjustments Based on Drug-Drug Interactions

Table 7. Established and Other Potentially Significant Drug Interactions: 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	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ lopinavir ↔ efavirenz ↔ nevirapine	A dose increase of KALETRA® to 533/133 mg (4 capsules or 6.5 mL) or 600/150 mg (given as three 200/50 mg tablets) 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 (**DOSAGE AND ADMINISTRATION**). NOTE: 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®. The effect of KALETRA® on both efavirenz and nevirapine was assessed in healthy volunteers. Although no significant interaction was apparent, due to study discontinuations, both studies had limited power to detect changes in efavirenz and nevirapine pharmacokinetics in the presence of KALETRA®.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ lopinavir	The safety and efficacy of this combination have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		KALETRA® tablets can be administered simultaneously with didanosine without food. For KALETRA® capsules and oral solution, it is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA® oral solution (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir*	↑ tenofovir ↔ lopinavir	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	Clinical Comment
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: amprenavir*, **	↑ amprenavir (amprenavir 750 mg b.i.d. + KALETRA® produces ↑ AUC, similar C_{max}, ↑ C_{min} relative to amprenavir 1200 mg b.i.d) ↓ lopinavir	KALETRA® at a dose of 400/100 mg, when co-administered with amprenavir, is not recommended. Safety and efficacy of increased doses of KALETRA® in combination with amprenavir have not been established. See (**Table 30** and **Table 31**). KALETRA® should not be administered once daily in combination with amprenavir. Amprenavir 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 (**DOSAGE AND ADMINISTRATION**).
HIV Protease Inhibitors: fosamprenavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse events has been observed with the co-administration of the medications. The safety and efficacy of this combination have not been established.
fosamprenavir/ritonavir*	↓ amprenavir ↑ lopinavir	The concomitant use of fosamprenavir/ritonavir and lopinavir/ritonavir is not recommended because of significant pharmacokinetic interactions. KALETRA® should not be administered once daily in combination with fosamprenavir. See (**DOSAGE AND ADMINISTRATION**).
HIV Protease Inhibitors: indinavir*	↑ indinavir (indinavir 600 mg b.i.d. + KALETRA® produces similar AUC, ↓ C_{max}, ↑ C_{min} relative to indinavir 800 mg t.i.d.) ↔ lopinavir	Decrease indinavir dose to 600 mg twice daily when co-administered with KALETRA® 400/100 mg twice daily. KALETRA® (capsules and tablets) once daily has not been studied in combination with indinavir.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
HIV Protease Inhibitors: nelfinavir*	↑ nelfinavir (nelfinavir 1000 mg b.i.d. + KALETRA® produces similar AUC, similar C_{max}, ↑ C_{min} relative to nelfinavir 1250 mg b.i.d.) ↑ M8 metabolite of nelfinavir ↓ lopinavir	A dose increase of KALETRA® to 533/133 mg (4 capsules or 6.5 mL) twice daily or 600/150 mg (given as three 200/50 mg tablets) 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. 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 (**DOSAGE AND ADMINISTRATION**).
HIV Protease Inhibitors: saquinavir*	↑ saquinavir (saquinavir 800 mg b.i.d. + KALETRA® produces ↑ AUC, ↑ C_{max}, ↑ C_{min} relative to saquinavir 1200 mg t.i.d.) ↔ lopinavir	Saquinavir 1000 mg twice daily may be considered when co-administered with KALETRA® 400/100 mg twice daily. KALETRA® (capsules and tablets) once daily has not been studied in combination with saquinavir.
HIV Protease Inhibitors: ritonavir*	↑ lopinavir	The safety and efficacy of this combination have not been established.
HIV Protease Inhibitors: tipranavir/ritonavir*	tipranavir/ritonavir + KALETRA® produces ↓ AUC and ↓ C_{min} of 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		
Antiarrhythmics: amiodarone, bepridil**, lidocaine (systemic), and quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA®, if available.
Anticancer Agents: vincristine, vinblastine	↑ anticancer agents	Potentially life-threatening adverse events usually associated with these anticancer agents have occurred as a result of having their serum concentrations increased when co-administered with lopinavir/ritonavir.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (International Normalized Ratio) be monitored.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
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 lopinavir/ritonavir resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with lopinavir/ritonavir.
Antidepressants: 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.
bupropion	↓ bupropion ↓ hydroxybupropion ↔ lopinavir	Concurrent administration of bupropion with lopinavir/ ritonavir will decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion).
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: ketoconazole*, itraconazole, voriconazole	↑ ketoconazole ↔ lopinavir ↑ itraconazole ↓ voriconazole	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. 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®. 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	Clinical Comment
Antimycobacterial: rifabutin*,	↑ rifabutin and rifabutin metabolite ↔ lopinavir	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	Due to the large reductions in lopinavir plasma concentrations observed in a study evaluating the combination of rifampin 600 mg once a day 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 lopinavir/ ritonavir co-administered with rifampin indicated higher incidences of liver and gastrointestinal toxicity.
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine**	↑ dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
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: dexamethasone,	↓ lopinavir	Use with caution. KALETRA® may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
fluticasone propionate	↑ fluticasone propionate	Concomitant use of ritonavir and fluticasone propionate can significantly increase fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
Disulfiram/ 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).
Erectile Dysfunction Agents - PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil lopinavir (study not done)	Particular caution should be used when prescribing sildenafil or tadalafil 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. Sildenafil may be used with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Concomitant use of sildenafil with KALETRA® is contraindicated in pulmonary arterial hypertension (PAH) patients. See (**CONTRAINDICATIONS**, **Table 1**). Tadalafil may be used with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Combination of vardenafil with KALETRA® is contraindicated. See (**CONTRAINDICATIONS**, **Table 1**).

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
HMG-CoA Reductase Inhibitors: atorvastatin*, rosuvastatin***, pravastatin*	↑ atorvastatin ↔ lopinavir ↑ rosuvastatin ↔ lopinavir ↑ pravastatin ↔ lopinavir	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 (**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 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® lopinavir/ritonavir. Note that an approximate 30% increase in pravastatin concentrations was observed and careful monitoring is warranted (See **Table** 31).
Immunosuppressants: cyclosporine, tacrolimus, rapamycin	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA®.
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.

* See **DETAILED PHARMACOLOGY** for Magnitude of Interaction, **Table 30** and **Table 31**.

** Product not marketed in Canada.

*** See Reference 8.

Definitions: b.i.d. = twice daily; t.i.d. = three times a day.

Other Drugs

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, omeprazole or ranitidine.

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

Flecainide and Propafenone

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®.

Drug-Herb Interactions

St. John's Wort (*Hypericum perforatum*)

Concomitant use of KALETRA® and St. John's wort (*Hypericum perforatum*), or products containing St. John's wort, is contraindictated. See (**CONTRAINDICATIONS**, **Table 1**). 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Do not use once daily administration of KALETRA® (lopinavir/ritonavir) in:
    - therapy-experienced patients
    - combination with efavirenz, nevirapine, fosamprenavir or nelfinavir
    - pediatric patients
- Concomitant therapy may affect the dose of KALETRA®. See (**DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment**, **Adults**, Concomitant Therapy) and (**DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment**, **Pediatric Patients**, Concomitant Therapy).
- For children 6 months to 12 years of age, the pediatric dose based on body weight or body surface area calculations.

Recommended Dose and Dosage Adjustment

- KALETRA® tablets may be taken with or without food.
- KALETRA® capsules and oral solution must be taken with food.
- KALETRA® tablets should be swallowed whole and not chewed, broken, or crushed.

The recommended oral dose of KALETRA® is as follows (please also refer to **INDICATIONS AND CLINICAL USE** and **ADVERSE REACTIONS**):

Adults

Therapy-Naïve Patients

Twice Daily Administration

- KALETRA® tablets 400/100 mg (given as two 200/50 mg tablets) twice daily taken with or without food.
- KALETRA® capsules or oral solution 400/100 mg (given as three 133.3/33.3 mg capsules or 5.0 mL, respectively) twice daily, taken with food to enhance bioavailability and minimize pharmacokinetic variability.

Once Daily Administration

- KALETRA® tablets 800/200 mg (given as four 200/50 mg tablets), taken once daily with or without food.
- KALETRA® capsules or oral solution 800/200 mg (given as six 133.3/33.3 mg capsules or 10.0 mL, respectively) taken once daily with food.

Therapy-Experienced Patients

- KALETRA® tablets 400/100 mg (given as two 200/50 mg tablets) twice daily with or without food.
- KALETRA® capsules or oral solution 400/100 mg (given as three 133.3/33.3 mg capsules or 5.0 mL, respectively) twice daily, taken with food.

Once daily administration of KALETRA® is not recommended in therapy-experienced patients.

Concomitant therapy:

Omeprazole and ranitidine:

- KALETRA® can be used in combination with acid-reducing agents (omeprazole and ranitidine) with no dose adjustment (see **Table 30**).

Efavirenz, nevirapine, amprenavir or nelfinavir:

- KALETRA® 400/100 mg tablets (given as two 200/50 mg tablets) can be used twice daily in combination with these drugs with no dose adjustment in antiretroviral-naïve

patients.

- A dose increase of KALETRA® tablets to 600/150 mg (given as three 200/50 mg tablets) twice daily may be considered when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). See (**DRUG INTERACTIONS**) and (**Table 7**).

- A dose increase of KALETRA® capsules or oral solution to 533/133 mg (given as four 133.3/33.3 mg capsules or 6.5 mL oral solution, respectively) twice daily taken with food may be considered when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir in the treatment of experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). See (**DRUG INTERACTIONS**) and (**Table 7**).

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 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 (**DRUG INTERACTIONS**, **Table 7**). The clinical significance in terms of safety and efficacy is not known.

KALETRA® tablets, capsules or oral solution should not be administered as a once daily regimen in combination with efavirenz, nevirapine, fosamprenavir or nelfinavir.

Pediatric Patients

Pediatric Patients (6 months to 18 years)

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

In children 6 months to 12 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.

Healthcare 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 **OVERDOSAGE**) and underdose. Prescribers should calculate the appropriate dose based on body weight or body surface area (BSA) recommendations in **Table 8**, **Table 9**, **Table 10**, **Table 11**, **Table 12** and **Table 13** for each individual child and depending on concomitant therapy.

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

Table 8. Pediatric Dosing Guidelines for KALETRA® Oral Solution† - Without Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir

Body Surface Area (m^2)*	Twice Daily Dose (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)

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

† KALETRA® oral solution should be taken with food.

Table 9. Pediatric Dosing Guidelines for KALETRA® 100/25 mg Tablets† - Without Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir

Body Surface Area (m^2)*	Recommended Number of 100/25 mg Tablets Twice Daily
0.4 to < 0.6	Tablets not recommended. Use oral solution.
≥ 0.6 to < 0.9	2 tablets (200/50 mg)
≥ 0.9 to < 1.4	3 tablets (300/75 mg)
≥ 1.4	4 tablets (400/100 mg)

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

† KALETRA® tablets may be taken with or without food.

Table 10. Pediatric Dosing Guidelines for KALETRA® Oral Solution and 100/25 mg Tablets – Without Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir

Weight (kg)	Twice Daily Dose (mg/kg)*	Volume of Oral Solution Twice Daily (80 mg lopinavir/20 mg ritonavir per mL)†	Number of 100/25 mg Tablets Twice Daily‡
7 to < 15 kg	**12 mg/kg**		Tablets are not recommended. Use oral solution.
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	2
> 20 to 25 kg		2.75 mL	2
> 25 to 30 kg		3.50 mL	3
> 30 to 35 kg		4.00 mL	3
> 35 to 40 kg		4.75 mL	4 (or two 200/50 mg tablets)
> 40 kg	See adult dosage recommendation		

* Dosing based on the lopinavir component of KALETRA® oral solution (80 mg/20 mg per mL).

† KALETRA® oral solution should be taken with food.

‡ KALETRA® tablets may be taken with or without food.

Note: Use adult dosage recommendation for children > 12 years of age.

Concomitant therapy: efaviranz, nevirapine, amprenavir or nelfinavir:

A dose increase of KALETRA® oral solution to 300/75 mg/m^2 twice daily taken with food, should be considered when used in combination with efavirenz, nevirapine, amprenavir, or nelfinavir in the treatment of experienced children 6 months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Children > 40 kg in weight should receive the adult dose (see **Table 10**). **Table 11** and **Table 12** contain dosing guidelines for KALETRA® oral solution and KALETRA® 100/25 mg tablets based on body surface area, respectively, and **Table 13** contains dosing guidelines for KALETRA® oral solution or the KALETRA® 100/25 mg tablets based on body weight, when used in combination with efavirenz, nevirapine, amprenavir, or nelfinavir in children. See (**DRUG INTERACTIONS**) and (**Table 7**).

Table 11. Pediatric Dosing Guidelines for KALETRA® Oral Solution† - With Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir

Body Surface Area (m^2)*	Twice Daily Dose (300/75 mg/m^2)
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)

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

† KALETRA® oral solution should be taken with food.

Table 12. Pediatric Dosing Guidelines for KALETRA® 100/25 mg Tablets† - With Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir

Body Surface Area (m^2)*	Recommended Number of 100/25 mg Tablets Twice Daily
0.4 to < 0.6	Tablets are not recommended. Use oral solution.
≥ 0.6 to < 0.8	2 tablet (200/50 mg)
≥ 0.8 to < 1.2	3 tablets (300/75 mg)
≥ 1.2	4 tablets (400/100 mg)

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

† KALETRA® tablets may be taken with or without food.

Table 13. Pediatric Dosing Guidelines for KALETRA® Oral Solution and 100/25 mg Tablets – With Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir

Weight (kg)	Twice Daily Dose (mg/kg)*	Volume of Oral Solution Twice Daily (80 mg lopinavir/20 mg ritonavir per mL)†	Number of 100/25 mg Tablets Twice Daily‡
7 to < 15 kg	**13 mg/kg**		Tablets are not recommended. Use oral solution.
7 to 10 kg		1.50 mL	
> 10 to <15 kg		2.00 mL	
15 to 40 kg	**11 mg/kg**		
15 to 20 kg		2.50 mL	2
> 20 to 25 kg		3.25 mL	3
> 25 to 30 kg		4.00 mL	3
> 30 to 35 kg		4.50 mL	4 (or two 200/50 mg tablets)
> 35 to 40 kg		5.00 mL	4 (or two 200/50 mg tablets)
> 40 kg	See adult dosage recommendation for concomitant therapy.		

* Dosing based on the lopinavir component of KALETRA® oral solution (80 mg/20 mg per mL).

† KALETRA® oral solution should be taken with food.

‡ KALETRA® tablets may be taken with or without food.

Note: Use adult dosage recommendation for children > 12 years of age.

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Overdoses with KALETRA® (lopinavir/ritonavir) oral solution have been reported. One of these reports described fatal cardiogenic shock in a 2.1 kg infant who received a single dose of 6.5 mL of KALETRA® oral solution nine days prior. However, a causal relationship between the overdose and the outcome could not be established. Healthcare professionals should be aware that KALETRA® oral solution is highly concentrated 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.

KALETRA® (lopinavir/ritonavir) oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

- 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.

ACTION AND CLINICAL PHARMACOLOGY

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® (lopinavir/ritonavir) is due to lopinavir.

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 five 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 five 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 I), 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 VI) appears to be consistent with that seen in adult patients (Study I).

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 one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least four 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 two 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 two PIs selected from nelfinavir, indinavir, saquinavir and ritonavir (Study VII). In this study, patients were initially randomized to receive one of two 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 14 shows the 48-week virologic response (HIV RNA < 400 and < 50 copies) according to susceptibility and number of genotypic mutations at baseline in 50 evaluable patients enrolled in the Study VII described above. Because this was a select patient population and the sample size was small, the data depicted in **Table 14** do not constitute definitive clinical susceptibility breakpoints. Additional data are needed to determine clinically significant breakpoints for KALETRA®.

Table 14. HIV RNA Response at Week 48 by Baseline KALETRA® Susceptibility and by Number of Protease Inhibitor-Associated Mutations[1] - Study VII

Lopinavir Susceptibility[2] 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)[3]	19/23 (83)
> 5	17/27 (63)	14/27 (52)

1: Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic.

2: Fold change in susceptibility from wild type.

3: 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 three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. **Table 15** 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 IV, V and VII (see below).

Table 15. 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[1]	Study IV	Study V	Study VII
	Single PI-experienced[2], NNRTI-naïve (n=130)	Single PI-experienced[3], NNRTI-naïve (n=56)	Multiple PI-experienced[4], NNRTI-naïve (n=50)
0 to 2	76/103 (74%)	34/45 (76%)	19/20 (95%)
3 to 5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	n/a	1/4 (25%)

1: Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

2: 43% indinavir, 42% nelfinavir, 10% ritonavir, 15% saquinavir.

3: 41% indinavir, 38% nelfinavir, 4% ritonavir, 16% saquinavir.

4: 86% indinavir, 54% nelfinavir, 80% ritonavir, 70% saquinavir.

Definitions: NNRTI = Non-nucleoside reverse transciptase inhibitor; PI = protease inhibitor; n/a=not applicable.

Pharmacodynamics

Viral Effects

Lopinavir is virologically ten-fold more active than ritonavir, with an EC_{50} of 0.07 mcg/mL against HIV-1_{IIIB} activity in MT_4 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 pretreatment 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

QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) differences in QTcF from placebo were 3.6 (6.3) msec and 13.1 (15.8) msec for the 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily KALETRA® regimen, respectively. The two regimens resulted in exposures on Day 3 which were approximately 1.5 and 3-fold higher than those observed with recommended once daily or twice daily KALETRA® doses at steady state. No subject experienced an increase in QTcF of > 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Mean change from baseline in PR interval of 11.6 to 31.2 msec was also noted in subjects receiving KALETRA® tablets in the same study on Day 3. Maximum PR interval was 286 msec and no second- or third-degree heart block was observed. See (**WARNINGS AND PRECAUTIONS**).

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 two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of KALETRA® 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.

Lopinavir is approximately 98 to 99% bound to plasma proteins. 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® capsule dose was due to parent drug.

After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. 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 nonfasting conditions (500 Kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA® co-formulated capsules and oral solution. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA® oral solution relative to the capsule formulation.

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 VIII and IX) 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. See (**CLINICAL TRIALS, Pivotal Comparative Bioavailability Studies**). 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 VIII) 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%. See (**CLINICAL TRIALS, Pivotal Comparative Bioavailability Studies**).

In a Phase 1, single-center, open-label, randomized, cross-over study (Study IX) 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 two 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. See (**CLINICAL TRIALS, Pivotal Comparative Bioavailability Studies**).

In a Phase 3, multicenter, open-label, randomized study (Study XI) 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 X) 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. See (**CLINICAL TRIALS, Pivotal Comparative Bioavailability Studies**).

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 VIII) 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 **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Absorption** and **CLINICAL TRIALS, Pivotal Comparative Bioavailability Studies**. KALETRA® tablets may therefore be taken with or without food.

KALETRA® Capsules

The effect of food on absorption of the KALETRA® capsule has been analyzed in three separate studies in healthy adults, each showing a consistent increase in lopinavir bioavailability when administered with food. 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 mean increases of 39 to 62% and 15 to 32% in lopinavir AUC_t and C_{max}, respectively, and mean increases in ritonavir AUC_t and C_{max} of 22 to 44% and no change to 31%, respectively, relative to fasting. Administration of the KALETRA® capsules with a moderate-fat meal reduced the pharmacokinetic variability of both lopinavir and ritonavir relative to administration under fasting conditions. To enhance bioavailability and minimize pharmacokinetic variability, KALETRA® capsules should be taken with 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.

Excretion

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 a day 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

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). KALETRA® once daily has not been evaluated in pediatric patients. See (**CLINICAL TRIALS, Study Results, Pediatric Use**).

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).

Geriatrics

Lopinavir pharmacokinetics has not been studied in elderly patients.

Gender

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.

Race

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 C_{max} 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 (**WARNINGS AND PRECAUTIONS**, **Hepatic/ Biliary/Pancreatic**).

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.

STORAGE AND STABILITY

KALETRA® Film-coated Tablets

Store KALETRA® film-coated tablets between 15 to 25°C. It is recommended that the product be stored and dispensed in the original container.

KALETRA® Soft Gel Capsules

Store KALETRA® soft gel capsules between 2 to 8°C (36° to 46°F) until dispensed. Avoid exposure to excessive heat. Product must be stored and dispensed in the original container. Refrigeration of KALETRA® soft gel capsules by the patient is not required if used within 42 days and stored below 25°C (77°F).

KALETRA® Oral Solution

Store KALETRA® oral solution between 2 to 8°C (36 to 46°F) 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 (77°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

KALETRA® Film-Coated Tablets

KALETRA® (lopinavir/ritonavir) tablets are available in two 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 embossed 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 embossed with the Abbott logo and the Abbo-Code KA. Each bottle contains 120 tablets.

Listing of Non-Medicinal Ingredients

Each 100/25 mg tablet contains 100 mg of lopinavir and 25 mg of ritonavir with the following non-medicinal ingredients: 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 200 mg of lopinavir and 50 mg of ritonavir with the following non-medicinal ingredients: 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.

KALETRA® Soft Gel Capsules

KALETRA® (lopinavir/ritonavir) capsules are orange soft gel capsules imprinted with the Abbott logo and the Abbo-Code PK. KALETRA® is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules. Each bottle contains 180 capsules.

Listing of Non-Medicinal Ingredients

Each capsule contains 133.3 mg of lopinavir and 33.3 mg of ritonavir with the following non-medicinal ingredients: butylated hydroxytoluene, FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, water.

KALETRA® Oral Solution

KALETRA® (lopinavir/ritonavir) 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.

Listing of Non-Medicinal Ingredients

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).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

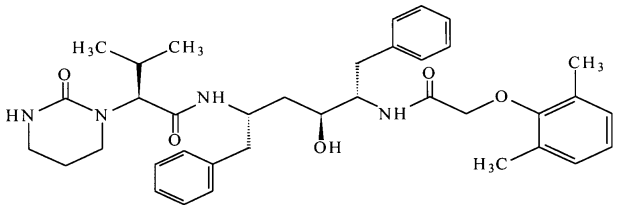
Lopinavir

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-ethylethyl)-2-oxo-1(2H)-pyrimidineacetamide

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

Structural formula:



Physicochemical properties: Lopinavir is a white to light tan powder.

Solubility: Lopinavir is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

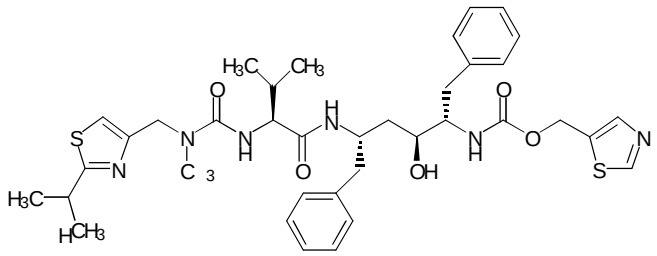
Ritonavir

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:	$C_{37}H_{48}N_6O_5S_2$	720.95

Structural formula:



Physicochemical properties: Ritonavir is a white to light tan powder.

Solubility: Ritonavir is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

CLINICAL TRIALS

Study Demographics and Trial Design

Table 16. Summary of Patient Demographics for Clinical Trials in Specific Indications

	Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Mean Age (Range)[1]	Gender Race (%M/F) (%C/O)[2]	Mean Baseline CD_4 Cell Count (Range)[3]	Mean Baseline Plasma HIV-1 RNA (Range)[4]
Patients Without Prior Antiretroviral Therapy	I	Randomized, Double-blinded, Multicentre	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)
	II (Evaluation KALETRA® at 3 dose levels)	Randomized, Blinded, Multicentre	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)
	III	Randomized, Open-label, Multicentre	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)[1]	Gender Race (%M/F) (%C/O)[2]	Mean Baseline CD_4 Cell Count (Range)[3]	Mean Baseline Plasma HIV-1 RNA (Range)[4]
Patients With Prior Antiretroviral Therapy	IV	Randomized, Open-label, Multicentre	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)
	V (Evaluation lopinavir/ ritonavir at 2 dose levels)	Randomized, Blinded, Multicentre	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	VI	Open-label, Multicentre	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% experi-enced)	5 (6 months - 12 yrs) (14% < 2yrs)	43/57 14/86	838	4.7

1: Measured in Years

2: % Male/Female, % Caucasian/Other

3: Measured in cells/mm^3

4: Measured in $\log_{10}$ copies/mL

Definitions: b.i.d. = twice daily; t.i.d.= three times a day; NRTI = nucleoside reverse transciptase inhibitor; PI = protease inhibitor; GRP = Group.

Study Results

Adult Use

Patients Without Prior Antiretroviral Therapy

Study I: KALETRA® capsules twice daily + stavudine + lamivudine compared to nelfinavir three times a day + stavudine + lamivudine.

Study I was a randomized, double-blind, multicentre trial comparing treatment with KALETRA® capsules (400/100 mg twice daily) plus stavudine and lamivudine *versus* nelfinavir (750 mg three times a day) plus 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 17**.

Table 17. Outcomes of Randomized Treatment Through Week 48 (Study I)

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

1: Patients achieved and maintained confirmed HIV RNA less than 400 copies/mL through Week 48.

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

3: 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 18**.

Table 18. Proportion of Responders Through Week 48 by Baseline Viral Load (Study I)

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

Definitions: D4T = stavudine; 3TC = lamivudine.

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

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

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 II: KALETRA® capsules twice daily + stavudine + lamivudine

Study II was a randomized, blinded, multicentre trial evaluating treatment with KALETRA® capsules at three 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) plus 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 19**), and the corresponding mean increase in CD_4 cell count was 501 cells/mm^3 (see **Table 20**). 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 (two consecutive rebound HIV-1 RNA values above 400 copies/mL, one 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 19. Summary of HIV-1 RNA Results (Study II)

	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 (Noncompleter=Failure)

Table 20. Mean Change from Baseline to Week 360 in CD_4 Cell Count by Baseline Value (Study II)

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.

Study III: KALETRA® capsules daily + tenofovir DF + emtricitabine compared to lopinavir/ritonavir twice daily + tenofovir DF + emtricitabine

Study III was a randomized, open-label, multicentre trial comparing treatment with KALETRA® capsules 800/200 mg once daily plus tenofovir DF and emtricitabine versus KALETRA® capsules 400/100 mg twice daily plus 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 21** and **Table 22**, 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 21. Virologic response Through Week 48 (Study III)*†

	Proportion of Subjects Responding < 50 Copies/mL ITT (FDA TLOVR)	
Week	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%

* Roche AMPLICOR HIV-1 MONITOR Assay

† 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 22. Outcomes of Randomized Treatment Through Week 48 (Study III)

Outcome	KALETRA® capsules 800/200 mg daily + TDF + FTC (N=115)	KALETRA® capsules 400/100 mg b.i.d. + TDF + FTC (N=75)
Responder*[1]	71%	65%
Virologic failure[2]	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[3]	7%	17%

* Corresponds to rates at Week 48 in **Table 21**.

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

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

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

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 XI: KALETRA® tablets once daily + tenofovir DF + emtricitabine compared to KALETRA® tablets twice daily + tenofovir DF + emtricitabine

Study XI was a randomized, open-label, multicenter trial comparing treatment with KALETRA® 800/200 mg once daily plus tenofovir DF and emtricitabine versus KALETRA® 400/100 mg twice daily plus tenofovir DF and emtricitabine in 664 antiretroviral treatment-naïve patients. Patients were randomized in a 1:1 ratio to receive either KALETRA® 800/200 mg once daily (n=333) or KALETRA® 400/100 mg twice daily (n=331). Further stratification within each group was 1:1 (tablet vs. capsule). Patients administered the capsule were switched to the tablet formulation at Week 8 and maintained on their randomized dosing schedule. Patients were administered emtricitabine 200 mg once daily and tenofovir DF 300 mg once daily. Mean age of patients enrolled was 39 years (range: 19 to 71); 75% were Caucasian, and 78% were male. Mean baseline 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 23**.

Table 23. Outcomes of Randomized Treatment Through Week 48 (Study XI)

Outcome[1]	KALETRA® tablets 800/200 mg daily + TDF + FTC (N=333)	KALETRA® tablets 400/100 mg b.i.d. + TDF + FTC (N=331)
Responder[2]	78 %	77 %
Virologic failure[3]	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[4]	8 %	12 %

1: Based on FDA Time to Loss of Virologic Response algorithm, a secondary endpoint for the study.

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

3: Includes confirmed viral rebound, failure to suppress and on study at Week 48, and discontinued due to insufficient viral response.

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

Through 48 weeks of therapy, 78% in the KALETRA® once daily arm and 77% in the KALETRA® twice daily arm achieved and maintained HIV-1 RNA < 50 copies/mL 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 IV: KALETRA® capsules twice daily + nevirapine + NRTIs compared to investigator-selected PI(s) + nevirapine + NRTIs

Study was a randomized, open-label, multicentre trial comparing treatment with KALETRA® capsules (400/100 mg twice daily) plus nevirapine and NRTIs versus investigator-selected PI(s) plus 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 24**.

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 24. Outcomes of Randomized Treatment Through Week 48 (Study IV)

Outcome	KALETRA® capsules 400/100 mg b.i.d. + nevirapine + NRTIs (N=148)	Investigator-selected PI(s) + nevirapine + NRTIs (N=140)
Responder*[1]	57%	33%
Virologic failure[2]	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[3]	14%	13%

* Corresponds to responses at Week 48.

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

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

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

Definition: NRTI = nucleoside reverse transciptase inhibitors; PI = protease inhibitor.

Study V: KALETRA® capsules twice daily + nevirapine + NRTIs

Study V was a randomized, blinded, multicentre trial evaluating treatment with KALETRA® capsules at two dose levels (400/100 mg twice daily and 400/200 mg twice daily) plus nevirapine (200 mg twice daily) and two 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 V, 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 two (3%) deaths.

Pediatric Use

Study VI: KALETRA® oral solution twice daily in antiretroviral-naïve and experienced pediatric patients

Study VI 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 plus up to two NRTIs.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of 5 years (range: 6 months to 12 years) with 14% less than 2 years. Mean baseline 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).

Pivotal Comparative Bioavailability Studies

Studies VIII and IX examined the relative bioavailability of lopinavir and ritonavir following single dose administration of 400/100 mg given as two KALETRA® 200/50 mg tablets and three KALETRA® 133.3/33.3 mg capsules using randomized, open-label, cross-over designs. Study VIII enrolled 63 healthy adults (46 males and 17 females) in a fasting/non-fasting design where one lot of the tablet was compared to one lot of the capsule. Study IX enrolled 48 healthy adults (34 males and 14 females) in a non-fasting design where two production scale lots of the tablet were compared to one lot of the capsule.

Table 25 summarizes the comparative bioavailability of the two formulations from single KALETRA® capsule and tablet doses under non-fasting (moderate-fat meal) conditions.

Table 25. Relative Bioavailability and 90% Confidence Intervals for Lopinavir and Ritonavir from Meta-Analysis of Studies VIII and IX (Moderate-Fat Meal Conditions) Following a Single 400/100 mg Dose: Tablet to Capsule Comparison

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	90% Confidence Interval
Lopinavir					
Tablet vs. Capsule	C_{max} (mcg/mL)	8.0 8.2 (26)	6.5 6.7 (29)	1.235	1.188-1.285
	AUC_t (mcg•h/mL)	95.8 100.5 (33)	80.9 86.1 (38)	1.184	1.131-1.239
	AUC_∞ (mcg•h/mL)	96.2 100.9 (33)	81.5 86.8 (38)	1.181	1.129-1.236
Ritonavir					
Tablet vs. Capsule	C_{max} (mcg/mL)	0.6 0.6 (42)	0.4 0.5 (58)	1.349	1.263-1.441
	AUC_t (mcg•h/mL)	4.3 4.7 (42)	3.6 4.0 (49)	1.202	1.146-1.261
	AUC_∞ (mcg•h/mL)	4.4 4.8 (41)	3.7 4.1 (48)	1.193	1.139-1.249

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Note: Includes two lots of the tablets and two lots of the capsules administered as a single 400/100 mg dose under moderate-fat meal conditions. KALETRA® capsules and tablets used in these studies are identical to KALETRA® capsules and tablets

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	90% Confidence Interval
available on the Canadian market.					

Table 26 summarizes the comparative bioavailability of the two formulations from single KALETRA® capsule and tablet doses under fasting and non-fasting conditions in Study VIII.

Table 26. Relative Bioavailability and 90% Confidence Intervals for Lopinavir and Ritonavir from Study VIII Following a Single 400/100 mg Dose: Tablet to Capsule Comparison

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	90% Confidence Interval
Lopinavir					
Tablet (Fasting) vs. Capsule (Moderate-Fat Meal)	C_{max} (mcg/mL)	6.95 7.2 (28)	6.3 6.6 (27)	1.101	1.032-1.175
	AUC_t (mcg•h/mL)	76.2 81.6 (37)	76.0 82.6 (35)	1.002	0.931-1.080
	AUC_∞ (mcg•h/mL)	76.5 82.0 (37)	76.5 83.1 (35)	1.000	0.929-1.077
Tablet (Moderate-Fat Meal) vs. Capsule (Moderate-Fat Meal)	C_{max} (mcg/mL)	8.2 8.4 (26)	6.3 6.6 (27)	1.295	1.230-1.362
	AUC_t (mcg•h/mL)	96.7 101.9 (33)	76.0 82.6 (35)	1.272	1.197-1.351
	AUC_∞ (mcg•h/mL)	97.1 102.3 (33)	76.5 83.1 (35)	1.269	1.195-1.348
Tablet (High-Fat Meal) vs. Capsule (Moderate-Fat Meal)	C_{max} (mcg/mL)	6.90 7.1 (25)	7.23 7.4 (21)	0.954	0.876-1.040
	AUC_t (mcg•h/mL)	86.6 88.3 (20)	85.5 88.5 (27)	1.012	0.924-1.108
	AUC_∞ (mcg•h/mL)	87.1 88.8 (20)	86.0 88.9 (27)	1.013	0.926-1.108
Tablet (Fasting) vs. Capsule (Fasting)#	C_{max} (mcg/mL)	7.0 7.2 (28)	4.8 5.3 (44)	1.457	1.314-1.615

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means[+]	90% Confidence Interval
	AUC_t (mcg•h/mL)	76.2 81.6 (37)	46.9 56.4 (56)	1.627	1.439-1.839
	AUC_∞ (mcg•h/mL)	76.5 82.0 (37)	47.4 56.9 (56)	1.616	1.431-1.824
Ritonavir					
Tablet (Fasting) vs. Capsule (Moderate-Fat Meal)	C_{max} (mcg/mL)	0.50 0.57 (49)	0.37 0.44 (56)	1.331	1.183-1.497
	AUC_t (mcg•h/mL)	3.52 4.08 (48)	3.20 3.80 (50)	1.098	1.006-1.199
	AUC_∞ (mcg•h/mL)	3.65 4.21 (46)	3.34 3.94 (48)	1.092	1.004-1.188
Tablet (Moderate-Fat Meal) vs. Capsule (Moderate-Fat Meal)	C_{max} (mcg/mL)	0.5 0.58 (45)	0.4 0.44 (56)	1.396	1.286-1.517
	AUC_t (mcg•h/mL)	4.1 4.65 (46)	3.2 3.80 (50)	1.270	1.189-1.356
	AUC_∞ (mcg•h/mL)	4.2 4.78 (45)	3.3 3.94 (48)	1.254	1.177-1.336
Tablet (High-Fat Meal) vs. Capsule (Moderate-Fat Meal)	C_{max} (mcg/mL)	0.5 30.57 (39)	0.47 0.53 (59)	1.147	0.987-1.333
	AUC_t (mcg•h/mL)	4.32 4.55 (34)	3.76 4.09 (42)	1.149	1.048-1.258
	AUC_∞ (mcg•h/mL)	4.4 44.68 (33)	3.91 4.23 (41)	1.136	1.040-1.240

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	90% Confidence Interval
Tablet (Fasting) vs. Capsule (Fasting)#	C_{max} (mcg/mL)	0.5 0.57 (49)	0.3 0.38 (67)	1.707	1.495-1.950
	AUC_t (mcg•h/mL)	3.5 4.08 (48)	2.2 2.86 (64)	1.579	1.402-1.778
	AUC_∞ (mcg•h/mL)	3.7 4.21 (46)	2.4 2.99 (61)	1.532	1.376-1.706

The relative bioavailability of the tablet administered under fasting conditions with the capsule administered under fasting conditions does not reflect recommended dosing conditions.

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Note: All formulations administered as a single 400/100 mg dose. KALETRA® capsules and tablets used in this study are identical to KALETRA® capsules and tablets available on the Canadian market.

Table 27 summarizes the comparative bioavailability of the two formulations from single KALETRA® capsule and tablet doses under non-fasting conditions in Study IX.

Table 27. Relative Bioavailability and 90% Confidence Intervals for Lopinavir and Ritonavir from Study IX (Moderate-Fat Meal Conditions) Following a Single 400/100 mg Dose: Tablet to Capsule Comparison

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	90% Confidence Interval
Lopinavir					
Tablet (Lot 1) vs. Capsule	C_{max} (mcg/mL)	8.1 8.29 (26)	6.6 6.92 (30)	1.227	1.158-1.300
	AUC_t (mcg•h/mL)	95.7 100.4 (33)	84.5 91.6 (39)	1.132	1.062-1.208
	AUC_∞ (mcg•h/mL)	96.2 101.0 (33)	85.2 92.5 (40)	1.129	1.059-1.204
Tablet (Lot 2) vs. Capsule	C_{max} (mcg/mL)	7.7 7.94 (26)	6.6 6.92 (30)	1.170	1.104-1.241
	AUC_t (mcg•h/mL)	93.2 98.7 (35)	84.5 91.6 (39)	1.102	1.034-1.176

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	90% Confidence Interval
	AUC_∞ (mcg•h/mL)	93.6 99.2 (35)	85.2 92.5 (40)	1.099	1.031-1.172
Ritonavir					
Tablet (Lot 1) vs. Capsule	C_{max} (mcg/mL)	0.6 0.63 (38)	0.4 0.51 (59)	1.378	1.242-1.530
	AUC_t (mcg•h/mL)	4.3 4.59 (37)	3.8 4.23 (48)	1.151	1.075-1.232
	AUC_∞ (mcg•h/mL)	4.5 4.72 (37)	3.9 4.35 (47)	1.148	1.075-1.226
Tablet (Lot 2) vs. Capsule	C_{max} (mcg/mL)	0.6 0.60 (43)	0.4 0.51 (59)	1.291	1.163-1.433
	AUC_t (mcg•h/mL)	4.3 4.64 (40)	3.8 4.23 (48)	1.152	1.076-1.234
	AUC_∞ (mcg•h/mL)	4.4 4.75 (40)	3.9 4.35 (47)	1.147	1.074-1.225

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Note: All formulations administered as a single 400/100 mg dose. KALETRA® capsules and tablets used in this study are identical to KALETRA® capsules and tablets available on the Canadian market.

Table 28 summarizes the comparative bioavailability from single tablet doses under fasting and non-fasting conditions in Study VIII.

Table 28. Relative Bioavailability and 90% Confidence Intervals for Lopinavir and Ritonavir from Study VIII Following a Single 400/100 mg Dose: Tablet Food Effect Comparison

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	90% Confidence Interval
Lopinavir					
Tablet (Moderate-Fat) vs. Tablet	C_{max} (mcg/mL)	8.2 8.38 (26)	7.0 7.16 (28)	1.176	1.111-1.244

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means[+]	90% Confidence Interval
(Fasting)	AUC_t (mcg•h/mL)	96.7 101.9 (33)	76.2 81.6 (37)	1.269	1.191-1.352
	AUC_∞ (mcg•h/mL)	97.1 102.3 (33)	76.5 82.0 (37)	1.269	1.191-1.352
Tablet (High-Fat Meal) vs. Tablet (Fasting)	C_{max} (mcg/mL)	6.9 7.08 (25)	7.0 7.40 (38)	0.993	0.877-1.124
	AUC_t (mcg•h/mL)	86.6 88.3 (20)	73.0 79.9 (45)	1.187	1.028-1.371
	AUC_∞ (mcg•h/mL)	87.1 88.8 (20)	73.3 80.2 (44)	1.189	1.029-1.373
Tablet (High-Fat Meal) vs. Tablet (Moderate-Fat Meal)	C_{max} (mcg/mL)	6.9 7.08 (25)	8.2 8.34 (21)	0.844	0.780-0.913
	AUC_t (mcg•h/mL)	86.6 88.3 (20)	94.3 96.8 (23)	0.918	0.859-0.982
	AUC_∞ (mcg•h/mL)	87.1 88.8 (20)	94.7 97.2 (23)	0.919	0.861-0.982
Ritonavir					
Tablet (Moderate-Fat) vs. Tablet (Fasting)	C_{max} (mcg/mL)	0.5 0.58 (45)	0.5 0.57 (49)	1.049	0.943-1.167
	AUC_t (mcg•h/mL)	4.1 4.65 (46)	3.5 4.08 (48)	1.156	1.066-1.253
	AUC_∞ (mcg•h/mL)	4.2 4.78 (45)	3.7 4.21 (46)	1.149	1.063-1.241
Tablet (High-Fat Meal) vs. Tablet (Fasting)	C_{max} (mcg/mL)	0.5 0.57 (39)	0.5 0.57 (59)	1.103	0.920-1.323
	AUC_t (mcg•h/mL)	4.3 4.55 (34)	3.5 3.99 (55)	1.247	1.071-1.453
	AUC_∞ (mcg•h/mL)	4.4 4.68 (33)	3.6 4.10 (54)	1.239	1.068-1.436
Tablet (High-Fat Meal) vs. Tablet (Moderate-Fat Meal)	C_{max} (mcg/mL)	0.5 0.57 (39)	0.6 0.60 (45)	0.973	0.853-1.109
	AUC_t (mcg•h/mL)	4.3 4.55 (34)	4.1 4.43 (38)	1.042	0.977-1.111

Regimen Test vs. Reference	Pharmacokinetic Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	90% Confidence Interval
	AUC_{∞} (mcg•h/mL)	4.4 4.68 (33)	4.3 4.56 (37)	1.040	0.977-1.107

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Note: All formulations administered as a single 400/100 mg dose. KALETRA® tablets used in this study are identical to KALETRA® tablets available on the Canadian market.

The average lopinavir T_{max} for the 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 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.

Study X examined the relative bioavailability of lopinavir and ritonavir following single dose administration of 400/100 mg given as four KALETRA® 100/25 mg tablets and given as two KALETRA® 200/50 mg tablets using a randomized, open-label cross-over design under fasting conditions in 44 healthy adults (35 males, 9 females).

Table 29 summarizes the comparative bioavailability of the two formulations from single KALETRA® 100/25 mg tablet and 200/50 mg tablet doses under fasting conditions:

Table 29. Relative Bioavailability and 90% Confidence Intervals for Lopinavir and Ritonavir from Study X Following a Single 400/100 mg Dose: 100/25 mg Tablet to 200/50 mg Tablet Comparison

Regimen Test vs. Reference	Parameter	Geometric Mean* Arithmetic Mean (CV%)		Relative Bioavailability	
		Test	Reference	Ratio of Geometric Means+	Confidence Interval (90%)
Lopinavir					
100/25 mg tablet vs. 200/50 mg tablet	C_{max} (mcg/mL)	5.36 5.66 (30%)	5.23 5.47 (31%)	1.03	0.964-1.090
	AUC_T (mcg•h/mL)	61.02 66.61 (38%)	58.50 62.33 (35%)	1.05	0.975-1.120
	AUC_I (mcg•h/mL)	61.22 66.89 (38%)	58.68 62.56 (36%)	1.05	0.975-1.120
	T_{max} (h)#	3.48 (50%)	3.59 (36%)		
	$T_{1/2}$ (h)#	2.74 (32%)	2.74 (31%)		
Ritonavir					
100/25 mg tablet vs. 200/50 mg tablet	C_{max} (mcg/mL)	0.37 0.42 (52%)	0.36 0.40 (47%)	1.04	0.943-1.139
	AUC_T (mcg•h/mL)	2.97 3.29 (43%)	2.89 3.14 (39%)	1.03	0.959-1.103
	AUC_I (mcg•h/mL)	3.01 3.33 (43%)	2.93 3.18 (39%)	1.03	0.959-1.102
	T_{max} (h)#	3.42 (53%)	3.31 (36%)		
	$T_{1/2}$ (h)#	5.08 (19%)	5.05 (18%)		

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

\# Expressed as arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

For details regarding the lopinavir/ritonavir pharmacokinetics refer to the **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics** section.

The effects of co-administration of KALETRA® on the AUC, C_{max} and C_{min} are summarized in **Table 30** (effect of other drugs on lopinavir) and **Table 31** (effect of KALETRA® on other drugs).

Effect of Co-Administered Drugs on Lopinavir

Table 30. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug (See Table 7 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}
Amprenavir[1]	750 b.i.d., 10 d	400/100 capsule b.i.d., 1 d	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin	20 daily, 4 d	400/100 capsule b.i.d., 4 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz[2]	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)

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	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)
	600 qHS, 9d	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[8]	700 b.i.d. plus ritonavir 100 b.i.d., 14 d	400/100 capsule b.i.d., 4 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole	200 single dose	400/100 capsule b.i.d., 6 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 b.i.d., 10 d	400/100 capsule b.i.d., 1 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)[3]	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[4]	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)
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)
Pravastatin	20 daily, 4 d	400/100 capsule b.i.d., 4 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Ranitidine	150 single dose	400/100 tablet 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)
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[7]	800/200 capsule b.i.d., 9 d[5]	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[6]	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 (**CONTRAINDICATIONS**) and (**DRUG INTERACTIONS**).		
Ritonavir[2]	100 b.i.d., 3 to 4 wk[3]	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[9]	300 mg daily, 14 d	400/100 capsule b.i.d., 14 d	24	NC†	NC†	NC†
Tipranavir/ ritonavir[3]	500/200 mg b.i.d., (28 doses)	400/100 capsule b.i.d., (27 doses)	21 69	0.53 (0.40, 0.69)[10]	0.45 (0.32, 0.63)[10]	0.30 (0.17, 0.51)[10] 0.48 (0.40, 0.58)[11]

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

1: KALETRA® at dosage of 400/100 mg should not be used with amprenavir.

2: The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

3: Study conducted in HIV-positive adult subjects.

4: Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.

5: 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.

6: 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.

7: 28% ≥ Grade 2 transaminases were noted in this study.

8: Data extracted from the fosamprenavir labelling.

9: Data extracted from the tenofovir labelling.

10: Intensive pharmacokinetic analysis

11: Drug levels obtained at 8 to 16 hrs post-dose.

* Parallel group design; n for KALETRA® + co-administered drug, n for KALETRA® alone.

† No Change

Definitions: b.i.d. = twice daily; d = day; wk = week; yr = year; qHS = every night.

Effect of KALETRA® on Co-Administered Drugs

Table 31. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA® (See Table 7 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 KALETRA®) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir[1]	1200 b.i.d., 14 d alone vs. 750 b.i.d., 10 d combo	400/100 capsule b.i.d., 21 d	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
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)
Desipramine[2]	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
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)
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)
Fosamprenavir[5]	700 b.i.d. plus 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[1]	800 t.i.d., 5 d alone fasting vs. 600 b.i.d., 10 d with KALETRA® nonfasting	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)
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)	NA
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
Nelfinavir[1]	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)

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}
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 7** for discussion of interaction.		
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)
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
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[3]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Saquinavir[1]	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®			0.98[4] (0.74, 1.30)	0.97[4] (0.73, 1.28)	0.95[4] (0.70, 1.29)
Rosuvastatin[6]	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)
Tenofovir[7]	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)

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®.

1: Ratio of parameters for amprenavir, indinavir, nelfinavir and saquinavir are not normalized for dose.

2: Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.

3: Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.

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}

4: Ratios are for saquinavir 1200 twice daily + KALETRA® vs. saquinavir 800 twice daily + KALETRA®.

5: Data extracted from the fosamprenavir labelling

6: 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).

7: Data extracted from the tenofovir labelling

* Parallel group design; n for KALETRA® + co-administered drug, n for co-administered drug alone.

† No Change

Definitions: b.i.d. = twice daily; d = day; wk = week; yr = year; qHS = every night; N/A = Not Available.

TOXICOLOGY

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

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.

Effects on the Liver

Mouse

A three-month oral maximum-tolerated dosage study was conducted in mice at dosages of 0, 20/10, 60/30 and 200/100 mg/kg/day. Hepatic toxicity observed in mice given 200/100 mg/kg/day (458/62 mcg•h/mL) was characterized by increased hepatic enzymes [alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT)] and liver weights and histopathological changes (cytoplasmic vacuolation, necrosis, subacute inflammation and hepatocytomegaly). Elevations of cholesterol and triglyceride levels were also noted at this dosage level. Increased liver weights and cholesterol levels occurred at a dosage of 60/30 mg/kg/day. No signs of toxicity were seen in the dosage group of 20/10 mg/kg/day with corresponding mean AUC values of 43/3 mcg•h/mL.

Rat

A lopinavir/ritonavir combination was administered to adult rats by oral gavage for a period of two weeks to six months. Hepatic changes observed in rats included increased cholesterol levels and elevated liver enzyme activities [ALT, alkaline phosphatase (ALP), GGT] and histopathologic lesions such as multinucleated hepatocytes, hepatocytomegaly, single cell necrosis and histiocytosis. These changes were observed at 50/25 mg/kg/day (mean AUC values of 73/8 mcg•h/mL) for six months. Ultrastructural evaluation of the liver revealed lysosomal inclusions in hepatocytes and minimal increase in smooth endoplasmic reticulum. Histopathologic alterations had not resolved in rats during the one-month of recovery. Due to an increase in serum ALT levels in male rats receiving 10/5 mg/kg/day, the no-hepatotoxic-effect dosage level in rats when administered for six months was considered to be less than 10/5 mg/kg/day (lopinavir/ritonavir), resulting in mean AUC values of approximately 18/1 mcg•h/mL.

A lopinavir/ritonavir combination was administered to neonatal rats (3 to 4 days old at the start of treatment) at dosages of 0, 10/5, 20/10 and 40/20 mg/kg/day for two weeks and to juvenile rats (16 days old at the start of treatment) at dosages of 0, 10/5, 30/15 and 100/50 mg/kg/day for four weeks. Changes in the liver (hepatocytomegaly) along with increases in liver weights, cholesterol levels and liver enzymes (ALT, GGT) of juvenile rats at dosages of 100/50 mg/kg/day which attained group mean AUC values of approximately 172/10 mcg•h/mL were generally similar to those observed in adult rats at the same dosages and similar drug exposures. However, significantly higher drug exposures (AUC values) were evident in neonates compared with adult rats at similar dosage levels. Less toxicity was seen in neonates relative to adults at similar drug exposures. A dosage level of 40/20 mg/kg/day (group mean AUC values of 140/13 mcg•h/mL) for two weeks in neonates produced only increased liver weights, but no microscopic findings in the liver or any other organs.

Dog

A lopinavir/ritonavir combination was administered by oral capsules to dogs for a period of two weeks to nine months. Dogs appeared to be less sensitive than rats to the hepatotoxic effects of the lopinavir/ritonavir combination. Although elevated liver enzyme activities (ALT, AST, ALP) and hepatocellular changes were seen in dogs, such changes were only observed in dogs receiving dosages of 70/35 to 100/50 mg/kg/day (mean AUC values of 189/65 mcg•h/mL) for three months or dosages of 45/15 mg/kg/day or greater for six months and achieving plasma exposures of approximately 206/53 mcg•h/mL. An increase in liver enzyme activities (ALP, ALT) and cell swelling in the liver occurred in dogs receiving 25/8 mg/kg/day (mean AUC values of 76/11 mcg•h/mL) for six months. The hepatocellular changes seen in dogs appeared to be reversible after a one-month recovery period. A dosage of 10/3 mg/kg/day (mean AUC values of 25/3 mcg•h/mL) for the lopinavir/ritonavir combination did not produce liver toxicity in dogs when treated for six months. In a nine-month study, only elevations in ALP and increased relative liver weights, but without any histopathologic changes were seen in dogs receiving dosages up to 50/20 mg/kg/day (mean AUC values of 78/39 mcg•h/mL).

Elevated GGT observed in repeated dose studies was limited to rodents only, and no increases in total bilirubin or urobilinogen were noted in rodents or dogs.

Cholestatic disease, with and without accompanying inflammation of the liver developed in anorectic, clinically compromised, high-dose dogs (AUC_{24} = 189/65 mcg•h/mL) in the three-month study.

Effects on the Thyroid

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 two to 26 weeks at dosages of 50/25 mg/kg/day or greater (mean AUC values of 65/14 mcg•h/mL or more). Neonatal and juvenile rats appeared to be less sensitive to the thyroid change produced by lopinavir/ritonavir than adult rats. No thyroid change was seen in neonatal rats receiving 40/20 mg/kg/day (mean AUC values of 140/13 mcg•h/mL) for two weeks, and thyroid change occurred in juvenile rats only when the dosage was up to 100/50 mg/kg/day (mean AUC values of 172/10 mcg•h/mL) for four weeks. All changes were reversible following a one-month recovery period. No effects on the thyroid gland were observed in any of the mouse (up to three months of treatment) or dog studies (up to nine months of treatment).

Effects on the Blood

Decreases in erythrocytic variables (erythrocyte count, hematocrit, hemoglobin) along with an increased incidence and/or severity of anisocytosis (erythrocytes of variable size) and poikilocytosis (erythrocytes with abnormal shapes) were observed in adult rats treated with lopinavir/ritonavir combination at 50/25 mg/kg/day or higher (mean AUC values of approximately 65/14 mcg•h/mL or more) for three to six months. Erythrocyte morphological changes in rats

persisted through the one-month recovery period. Similar erythrocytic changes also occurred in one female dog that received dosages of 45/15 to 60/20 mg/kg/day (mean AUC values of approximately 205/53 mcg•h/mL) for six months. Erythrocytic changes were not detected in mice that received the drug combination at dosages up to 200/100 mg/kg/day (mean AUCs = 458/62 mcg•h/mL) for three months or in dogs given the drug combination at dosages up to 50/25 mg/kg/day (mean AUCs = 78/39 mcg•h/mL) for nine months. Elevations of clotting times (APTT) were observed in rats in the three-month study at systemic exposure of 161/13 mcg•h/mL and in male rats in the six-month study at systemic exposure 56/5.2 mcg•h/mL.

Effects on the Kidney and Spleen

No kidney changes were observed in rat or dog studies with durations through six months or in dogs treated for nine months. Changes in kidney (microvesicular cytoplasmic vacuolation) occurred only in mice that received a combination dosage of 200/100 mg/kg/day (mean AUCs = 458/62 mcg•h/mL) for three months. Changes in spleen (histiocytosis and increased spleen weight) were limited to rats receiving combination dosages of 50/25 mg/kg/day or higher (mean AUCs of 73/8 mcg•h/mL or greater) for six months.

Effects on the Gastrointestinal Tract and Associated ECG Changes

The most sensitive indication of toxicity in dogs that received lopinavir/ritonavir combination was gastrointestinal (GI) distress consisting of emesis, diarrhea and/or loose stools. Dosage-related GI distress occurred generally within 1 to 2 hours after dosing at all dosages tested in the repeated dose studies. In the three-month toxicity study, moderate to severe GI distress occurred in dogs receiving the high dosages of 70/35 to 100/50 mg/kg/day (mean AUCs = 189/65 mcg•h/mL), subsequently hypokalemia, hyponatremia, hypochloridemia and variable blood acid-base imbalances were observed in the affected dogs.

ECG changes occurred in dogs at systemic exposure approximately equal and higher than exposure of humans at the recommended dose for three months. Prominent U waves were the primary ECG changes seen in the affected dogs. These changes are considered to be related to hypokalemia rather that direct cardiac toxicity.

Effects on the Testis

Testicular degeneration, generally classified as minimal or mild, was observed in dogs that received the drug combination at dosages of 10/3 to 60/20 mg/kg/day (mean AUC values of 20/2 to 206/53 mcg•h/mL) for six months. Features of the degeneration included loss of germ cells, germ cell degeneration and tubular vacuolization. The incidence and severity of testicular degeneration did not appear to be related to dosage or to correlate with the systemic drug exposures. In addition, no testicular changes were seen in dogs receiving the drug combination for nine months at dosages up to 50/25 mg/kg/day (mean AUC values of 78/39 mcg•h/mL). Bilateral testicular degeneration was also noted in male dogs receiving ritonavir alone at dosages of 50 mg/kg/day (mean AUCs = 64 mcg•h/mL) or greater, for six months or longer.

Effects on Serum Cholesterol and Triglycerides

Elevations in serum cholesterol levels were seen in mice and rats, and an increase in triglyceride levels was limited to mice that received the drug combination. No effects on cholesterol or triglycerides occurred in dogs receiving the drug combination for up to nine months. Increases in cholesterol and triglycerides occurred in mice receiving a combination dosage of 100/50 mg/kg/day (mean AUCs = 292/29 mcg•h/mL) for two weeks or dosages of ≥ 60/30 mg/kg/day (mean AUCs = 121/12 mcg•h/mL) for three months. Increased cholesterol levels were evident in juvenile rats receiving dosages of ≥ 30/15 mg/kg/day (mean AUCs = 62/3 mcg•h/mL) for four weeks and in adult rats given dosages of ≥ 50/25 mg/kg/day (mean AUCs of 65/7 to 73/8 mcg•h/mL) for three or six months. The elevations of cholesterol levels were considered possibly secondary to hepatic effects.

Mutagenicity and Carcinogenicity

Long-term carcinogenicity studies of up to two 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.

Reproduction and Teratology

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 postdose. 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 postdose to a mean value of 0.026 mcg equivalents [^{14}C]-lopinavir/g at 24 hours postdose.

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PART III: CONSUMER INFORMATION

PrKALETRA® tablets
lopinavir/ritonavir

This leaflet is PART III of a three-part "Product Monograph" published when KALETRA® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about KALETRA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- KALETRA® is for adults and children 6 months of age or older who are infected with the human immunodeficiency virus (HIV), the virus which causes AIDS.
- KALETRA® is prescribed for use in combination with other antiretroviral medicines.

What it does:

KALETRA® is an inhibitor of the HIV protease enzyme. It helps control HIV infection by inhibiting or interfering with the protease enzyme that HIV needs to multiply.

KALETRA® is not a cure for HIV infection or AIDS. People taking KALETRA® may still develop infections or other serious illnesses associated with HIV disease and 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.

When it should not be used:

Do not take KALETRA® if you/your child:

- are allergic to lopinavir, ritonavir or to any of the non-medicinal ingredients in KALETRA®. (Refer to the subheading "**What the important non-medicinal ingredients are**" for a complete listing).
- are currently taking any of the following medicines, because they can cause serious problems or death if taken with KALETRA®:
  - ergotamine,dihydroergotamine (used to treat headaches), ergonovine, methylergonovine* (used after labor and delivery), such as Cafergot®, Migranal®, D.H.E. 45®, Ergotrate® Maleate*, Methergine™*, and others;
  - triazolam, midazolam - used to relieve anxiety and/or trouble sleeping;
  - astemizole* (e.g. Hismanal®), terfenadine* (e.g. Seldane®) - used to relieve allergy symptoms;
  - pimozide (e.g. Orap®) - used to treat schizophrenia;
  - cisapride* (e.g. Prepulsid®) - used to relieve certain stomach problems;
- are currently taking rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®. Rifampin may lower the amount of KALETRA® in your blood and make it less effective.
- are currently taking St. John's wort (*Hypericum perforatum*), a herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease KALETRA® levels and lead to increased viral load and possible resistance to KALETRA® or cross-resistance to other anti-HIV medicines.
- are currently taking the cholesterol-lowering medicines lovastatin (e.g. Mevacor®) or simvastatin (e.g. Zocor®) because of possible serious reactions. Talk to your doctor before you take any cholesterol-lowering medicines with KALETRA®.
- are currently taking the PDE5 Inhibitors vardenafil (Levitra®), use to treat erectile dysfunction, or sildenafil (Revatio®), used for the treatment of pulmonary arterial hypertension (PAH). These drugs may increase the risk of hypotension (low blood pressure), syncope (fainting), visual changes and prolonged erection.
- are currently taking salmeterol, also known as Advair® and Serevent®. Salmeterol may increase the risk of cardiovascular (heart) adverse events.

* **Products not marketed in Canada.**

- are currently taking any of these medications; your doctor may switch your medication.

What the medicinal ingredients are:

lopinavir and ritonavir

What the important non-medicinal ingredients are:

KALETRA® 100/25 mg tablets also contain colloidal silicon dioxide, copovidone, polyethylene glycol 3350, polyvinyl alcohol, sodium stearyl fumarate, sorbitan monolaurate, talc, titanium dioxide, yellow ferric oxide E172.

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

What dosage forms it comes in:

KALETRA® is available as film-coated tablets containing the following combinations of lopinavir and ritonavir: 100mg/25 mg; 200 mg/50 mg.

KALETRA® is also available as a soft gel capsule containing 133.3 mg of lopinavir and 33.3 mg of ritonavir.

KALETRA® is also available as an oral solution. Each mL of KALETRA® contains 80 mg of lopinavir and 20 mg of ritonavir.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Tell your doctor if you or your child develops symptoms such as:

- **nausea**
- **vomiting**
- **abdominal pain.**

These may be signs of problems with your pancreas (pancreatitis). Your doctor must decide if these are related to pancreatitis and what to do about them.

BEFORE you use KALETRA® talk to your doctor or pharmacist if:

- You/your child have liver problems or are infected with Hepatitis B or Hepatitis C
- You/your child have diabetes, or symptoms such as frequent urination, and/or increase in thirst
- You/your child have hemophilia. Patients taking KALETRA® may have increased bleeding
- You/your child are taking or planning to take other medicines, **including prescription, herbal and other medicines** you can buy without a prescription
- You have heart disease or heart condition, including conditions of Congenital Long QT Syndrome
- You have low potassium levels in your blood.
- You are pregnant or breast-feeding. Pregnant or breast-feeding mothers should not take KALETRA® unless specifically directed by the doctor. Be sure to tell your doctor immediately if you are or may be pregnant or if you are breast-feeding a baby. It is recommended that HIV-infected women should not breast-feed their infants because of the possibility your baby can be infected with HIV through your breast milk

- Changes in body fat have been seen in some patients taking antiretroviral therapy. See **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**.

INTERACTIONS WITH THIS MEDICATION

KALETRA® may interact with certain other medications with possible clinical effects. The use of the following medicines together with KALETRA® should only take place on the basis of medical advice:

- medicines used to treat erectile dysfunction such as sildenafil (e.g. Viagra®) or tadalafil (e.g. Cialis®). Vardenafil (e.g. Levitra®) should not be taken with KALETRA®;
- medicines used to lower blood cholesterol such as rosuvastatin (e.g. Crestor®), atorvastatin (e.g. Lipitor®). Lovastatin (e.g. Mevacor®) or simvastatin (e.g. Zocor®) should not be taken with KALETRA®;
- some medicines affecting the immune system such as cyclosporin, sirolimus (e.g. Rapamune®) and tacrolimus;
- some medicines used to treat seasonal allergies and ear and eye infections such as dexamethasone and fluticasone propionate (e.g. Flonase®);
- contraceptives used to prevent pregnancy (e.g. ethinyl estradiol);
- medicines used to treat AIDS and related infections such as amprenavir* (e.g. Agenerase®), fosamprenavir (e.g. Telzir®), indinavir (e.g. Crixivan®), nelfinavir (e.g. Viracept®), saquinavir (e.g. Invirase®), didanosine (e.g. Videx®), tenofovir (e.g. Viread®) and rifabutin (e.g. Mycobutin®);
- medicines used to treat depression such as trazodone (e.g. Desyrel®) and bupropion (e.g. Wellbutrin® SR);
- certain heart medicines such as calcium channel antagonists including felodipine (e.g. Plendil®), nifedipine (e.g. Adalat®) and nicardipine* (e.g. Cardene®);
- medicines used to correct heart rhythm such as amiodarone (e.g. Cordarone®), flecainide (e.g. Tambocor®), bepridil* (e.g. Vascor®), systemic lidocaine, propafenone hydrochloride (e.g. Rythmol®), quinidine and digoxin;
- antifungals such as ketoconazole (e.g. Nizoral®), itraconazole (e.g. Sporanox®) and voriconazole (e.g. Vfend®);
- morphine-like medicines (e.g. methadone);
- anticonvulsants such as carbamazepine (e.g Tegretol®), phenytoin (e.g. Dilantin®) and phenobarbital;
- efavirenz (e.g. Sustiva™), nevirapine (e.g. Viramune®), amprenavir* (e.g. Agenerase®) or nelfinavir (e.g. Viracept®);
- warfarin and certain antibiotics such as rifabutin (e.g. Mycobutin®) and clarithromycin (e.g. Biaxin®);
- medicines used to treat cancer (e.g. vincristine, vinblastine).

*** Product not available in Canada.**

Patients taking KALETRA® should not take products containing St. John's Wort (*Hypericum perforatum*) as this may stop KALETRA® from working properly.

KALETRA® can be taken with acid reducing agents (such as omeprazole and ranitidine) with no dose adjustment.

PROPER USE OF THIS MEDICATION

It is important that you/your child take KALETRA® every day exactly as your doctor prescribed it. Even if you feel better, do not stop taking KALETRA® without talking to your doctor. Using

KALETRA® as recommended should give you the best chance to delay the development of resistance to the product.

It is therefore important that you remain under the supervision of your doctor while taking KALETRA®.

Usual dose:

The usual dose for adults is two 200/50 mg tablets (400/100 mg) twice a day (morning and night), in combination with other anti-HIV medicines. The doctor may prescribe KALETRA® as four 200/50 mg tablets (800/200 mg) once daily in combination with other anti-HIV medicines for some patients who have not taken anti-HIV medications in the past. KALETRA® should not be administered once daily in therapy experienced patients.

The dose for children from 6 months to 12 years of age will be determined by your doctor based on the child's height and weight. KALETRA® should not be administered once daily in pediatric patients less than 18 years of age.

KALETRA® tablets (all strengths) can be taken with or without food. KALETRA® tablets should be swallowed whole and not chewed, broken, or crushed.

Overdose:

If you/your child realize you have taken more KALETRA® than you were supposed to, contact your doctor or local poison control centre right away. If you cannot reach your/your child's doctor, go to the hospital.

Missed Dose:

If you/your child miss a dose of KALETRA®, it should be taken as soon as possible, and the next scheduled dose taken at its regular time. If it is almost time for your/your child's next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most commonly reported side effects of KALETRA® are abdominal pain, diarrhea (abnormal stool, and/or bowel movement), feeling weak or tired, headache, nausea, vomiting and rash.

- If you have liver disease such as Hepatitis B and Hepatitis C, taking KALETRA® may worsen your liver disease.
- Some patients have large increases in triglycerides and cholesterol (forms of fat that are found in your blood).
- Diabetes and high blood sugar (hyperglycemia) may occur in patients taking protease inhibitors such as KALETRA®. Symptoms of diabetes or high blood sugar may include frequent urination or increased thirst. Let your doctor know if you have or develop these symptoms while taking KALETRA®.
- Some patients with hemophilia have increased bleeding with protease inhibitors.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breasts, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Diarrhea	√		
	Rash	√		
	Headache	√		
	Nausea	√		
	Vomiting	√		
	tingling feeling in hands, feet and around lips	√		
Uncommon	chest pain		√	
	Pancreatitis		√	
	- abdominal pain		√	
	- nausea		√	
	- vomiting		√	

This is not a complete list of side effects. For any unexpected effects while taking KALETRA®, contact your doctor or pharmacist.

HOW TO STORE IT

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

KALETRA® film-coated tablets should be stored at 15 to 25°C. It is recommended that the product be stored and dispensed in the original container.

It is important to keep KALETRA® in the original package. Do not transfer to any other container.

Do not use after the expiry date stated on the pack.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at: www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678—6789
  - Mail to : Canada Vigilance Program
  Health Canada
  Postal Locator 0701C
  Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

http://www.abbott.ca
or by contacting the sponsor, Abbott Laboratories, Limited, Saint-Laurent, Qc H4S 1Z1 at:
1-800-699-9948

This leaflet was prepared by Abbott Laboratories, Limited.

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Adalat®, Agenerase®, Advair®, Cafergot®, Cardene®, Cordarone®, Crestor®, Cialis®, Crixivan®, Desyrel®, D.H.E. 45®, Dilantin®, Ergotrate® Maleate, Flonase®, Halcion®, Hismanal®, Levitra®, Lipitor®, Invirase®, Mevacor®, Migranal®, Mycobutin®, Nizoal®, Orap®, Plendil®, Prepulsid®, Rapamune®, Revatio®, Rifadin®, Rifater®, Rifamate®, Rimactane®, Seldane®, Serevent®, Sporanox®, Sustiva™, Tambocor®, Tegretol®, Telzir®, Vascor®, Versed®, Vfend®, Videx®, Viracept®, Viramune®, Viread®, Viagra®, Wellbutrin® SR, and Zocor® are trademarks of their respective owners and are not trademarks of Abbott Laboratories, Limited.

PART III: CONSUMER INFORMATION

PrKALETRA® soft gel capsules
lopinavir/ritonavir

This leaflet is PART III of a three-part "Product Monograph" published when KALETRA® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about KALETRA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- KALETRA® is for adults and children 6 months of age or older who are infected with the human immunodeficiency virus (HIV), the virus which causes AIDS.
- KALETRA® is prescribed for use in combination with other antiretroviral medicines.

What it does:

KALETRA® is an inhibitor of the HIV protease enzyme. It helps control HIV infection by inhibiting or interfering with the protease enzyme that HIV needs to multiply.

KALETRA® is not a cure for HIV infection or AIDS. People taking KALETRA® may still develop infections or other serious illnesses associated with HIV disease and 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.

When it should not be used:

Do not take KALETRA® if you/your child:

- are allergic to lopinavir, ritonavir or to any of the non-medicinal ingredients in KALETRA®. (Refer to the subheading "**What the important non-medicinal ingredients are**" for a complete listing).
- are currently taking any of the following medicines, because they can cause serious problems or death if taken with KALETRA®:
  - ergotamine,dihydroergotamine (used to treat headaches), ergonovine, methylergonovine* (used after labor and delivery), such as Cafergot®, Migranal®, D.H.E. 45®, Ergotrate® Maleate*, Methergine™*, and others;
  - triazolam, midazolam - used to relieve anxiety and/or trouble sleeping;
  - astemizole* (e.g. Hismanal®), terfenadine* (e.g. Seldane®) - used to relieve allergy symptoms;
  - pimozide (e.g. Orap®) - used to treat schizophrenia;
  - cisapride* (e.g. Prepulsid®) - used to relieve certain stomach problems;
- are currently taking rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®. Rifampin may lower the amount of KALETRA® in your blood and make it less effective.
- are currently taking St. John's wort (*Hypericum perforatum*), a herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease KALETRA® levels and lead to increased viral load and possible resistance to KALETRA® or cross-resistance to other anti-HIV medicines.
- are currently taking the cholesterol-lowering medicines lovastatin (e.g. Mevacor®) or simvastatin (e.g. Zocor®) because of possible serious reactions. Talk to your doctor before you take any cholesterol-lowering medicines with KALETRA®.
- are currently taking the PDE5 Inhibitors vardenafil (Levitra®), use to treat erectile dysfunction, or sildenafil (Revatio®), used for the treatment of pulmonary arterial hypertension (PAH). These drugs may increase the risk of hypotension (low blood pressure), syncope (fainting), visual changes and prolonged erection.
- are currently taking salmeterol, also known as Advair® and Serevent®. Salmeterol may increase the risk of cardiovascular (heart) adverse events.

* **Products not marketed in Canada.**

- are currently taking any of these medications; your doctor may switch your medication.

What the medicinal ingredients are:

lopinavir and ritonavir

What the important non-medicinal ingredients are:

KALETRA® capsules also contain butylated hydroxytoluene, FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, and titanium dioxide.

What dosage forms it comes in:

KALETRA® is available as a soft gel capsule containing 133.3 mg of lopinavir and 33.3 mg of ritonavir.

KALETRA® is also available as film-coated tablets containing the following combinations of lopinavir and ritonavir: 100mg/25 mg; 200 mg/50 mg.

KALETRA® is also available as an oral solution. Each mL of KALETRA® contains 80 mg of lopinavir and 20 mg of ritonavir.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Tell your doctor if you or your child develops symptoms such as:

- **nausea**
- **vomiting**
- **abdominal pain.**

These may be signs of problems with your pancreas (pancreatitis). Your doctor must decide if these are related to pancreatitis and what to do about them.

BEFORE you use KALETRA® talk to your doctor or pharmacist if:

- You/your child have liver problems or are infected with Hepatitis B or Hepatitis C
- You/your child have diabetes, or symptoms such as frequent urination, and/or increase in thirst
- You/your child have hemophilia. Patients taking KALETRA® may have increased bleeding
- You/your child are taking or planning to take other medicines, **including prescription, herbal and other medicines** you can buy without a prescription
- You have heart disease or heart condition, including conditions of Congenital Long QT Syndrome
- You have low potassium levels in your blood
- You are pregnant or breast-feeding. Pregnant or breast-feeding mothers should not take KALETRA® unless specifically directed by the doctor. Be sure to tell your doctor immediately if you are or may be pregnant or if you are breast-feeding a baby. It is recommended that HIV-infected women should not breast-feed their infants because of the possibility your baby can be infected with HIV through your breast milk

- Changes in body fat have been seen in some patients taking antiretroviral therapy. See **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**.

INTERACTIONS WITH THIS MEDICATION

KALETRA® may interact with certain other medications with possible clinical effects. The use of the following medicines together with KALETRA® should only take place on the basis of medical advice:

- medicines used to treat erectile dysfunction such as sildenafil (e.g. Viagra®) or tadalafil (e.g. Cialis®). Vardenafil (e.g. Levitra®) should not be taken with KALETRA®;
- medicines used to lower blood cholesterol such as rosuvastatin (e.g. Crestor®), atorvastatin (e.g. Lipitor®). Lovastatin (e.g. Mevacor®) or simvastatin (e.g. Zocor®) should not be taken with KALETRA®;
- some medicines affecting the immune system such as cyclosporin, sirolimus (e.g. Rapamune®) and tacrolimus;
- some medicines used to treat seasonal allergies and ear and eye infections such as dexamethasone and fluticasone propionate (e.g. Flonase®);
- contraceptives used to prevent pregnancy (e.g. ethinyl estradiol);
- medicines used to treat AIDS and related infections such as amprenavir* (e.g. Agenerase®), fosamprenavir (e.g. Telzir®), indinavir (e.g. Crixivan®), nelfinavir (e.g. Viracept®), saquinavir (e.g. Invirase®), didanosine (e.g. Videx®), tenofovir (e.g. Viread®) and rifabutin (e.g. Mycobutin®);
- medicines used to treat depression such as trazodone (e.g. Desyrel®), and bupropion (e.g. Wellbutrin® SR);
- certain heart medicines such as calcium channel antagonists including felodipine (e.g. Plendil®), nifedipine (e.g. Adalat®) and nicardipine* (e.g. Cardene®);
- medicines used to correct heart rhythm such as amiodarone (e.g. Cordarone®), flecainide (e.g. Tambocor®), bepridil* (e.g. Vascor®), systemic lidocaine, propafenone hydrochloride (e.g. Rythmol®), quinidine and digoxin;
- antifungals such as ketoconazole (e.g. Nizoral®), itraconazole (e.g. Sporanox®) and voriconazole (e.g. Vfend®);
- morphine-like medicines (e.g. methadone);
- anticonvulsants such as carbamazepine (e.g Tegretol®), phenytoin (e.g. Dilantin®) and phenobarbital;
- efavirenz (e.g. Sustiva™), nevirapine (e.g. Viramune®), amprenavir* (e.g. Agenerase®) or nelfinavir (e.g. Viracept®);
- warfarin and certain antibiotics such as rifabutin (e.g. Mycobutin®) and clarithromycin (e.g. Biaxin®);
- medicines used to treat cancer (e.g. vincristine, vinblastine).

*** Product not available in Canada.**

Patients taking KALETRA® should not take products containing St. John's Wort (*Hypericum perforatum*) as this may stop KALETRA® from working properly.

KALETRA® can be taken with acid reducing agents (such as omeprazole and ranitidine) with no dose adjustment.

PROPER USE OF THIS MEDICATION

It is important that you/your child take KALETRA® every day exactly as your doctor prescribed it. Even if you feel better, do not stop taking KALETRA® without talking to your doctor. Using KALETRA® as recommended should give you the best chance to delay the development of resistance to the product.

It is therefore important that you remain under the supervision of your doctor while taking KALETRA®.

Usual dose:

The usual dose for adults is 3 capsules (400/100 mg) twice a day (morning and night), in combination with other anti-HIV medicines. The doctor may prescribe KALETRA® as 6 capsules (800/200 mg) once daily in combination with other anti-HIV medicines for some patients who have not taken anti-HIV medications in the past. KALETRA® should not be administered once daily in therapy experienced patients.

The dose for children from 6 months to 12 years of age will be determined by your doctor based on the child's height and weight. KALETRA® should not be administered once daily in pediatric patients less than 18 years of age.

Take KALETRA® capsules with food to help it work better.

Overdose:

If you/your child realize you have taken more KALETRA® than you were supposed to, contact your doctor or local poison control centre right away. If you cannot reach your/your child's doctor, go to the hospital.

Missed Dose:

If you/your child miss a dose of KALETRA®, it should be taken as soon as possible, and the next scheduled dose taken at its regular time. If it is almost time for your/your child's next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most commonly reported side effects of KALETRA® are abdominal pain, diarrhea (abnormal stool, and/or bowel movement), feeling weak or tired, headache, nausea, vomiting and rash.

- If you have liver disease such as Hepatitis B and Hepatitis C, taking KALETRA® may worsen your liver disease.
- Some patients have large increases in triglycerides and cholesterol (forms of fat that are found in your blood).
- Diabetes and high blood sugar (hyperglycemia) may occur in patients taking protease inhibitors such as KALETRA®. Symptoms of diabetes or high blood sugar may include frequent urination or increased thirst. Let your doctor know if you have or develop these symptoms while taking KALETRA®.
- Some patients with hemophilia have increased bleeding with protease inhibitors.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breasts, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Diarrhea	√		
	Rash	√		
	Headache	√		
	Nausea	√		
	Vomiting	√		
	tingling feeling in hands, feet and around lips	√		
Uncommon	chest pain		√	
	Pancreatitis		√	
	- abdominal pain		√	
	- nausea		√	
	- vomiting		√	

This is not a complete list of side effects. For any unexpected effects while taking KALETRA®, contact your doctor or pharmacist.

HOW TO STORE IT

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

KALETRA® soft gel capsules should be stored at 2 to 8°C in a refrigerator. If you keep KALETRA® outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). Avoid exposure to excessive heat.

It is important to keep KALETRA® in the original package. Do not transfer to any other container.

Do not use after the expiry date stated on the pack.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at: www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678—6789
  - Mail to : Canada Vigilance Program
  Health Canada
  Postal Locator 0701C
  Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

http://www.abbott.ca
or by contacting the sponsor, Abbott Laboratories, Limited, Saint-Laurent, Qc H4S 1Z1 at:
1-800-699-9948

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PART III: CONSUMER INFORMATION

PrKALETRA® oral solution
lopinavir/ritonavir

This leaflet is PART III of a three-part "Product Monograph" published when KALETRA® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about KALETRA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- KALETRA® is for adults and children 6 months of age or older who are infected with the human immunodeficiency virus (HIV), the virus which causes AIDS.
- KALETRA® is prescribed for use in combination with other antiretroviral medicines.

What it does:

KALETRA® is an inhibitor of the HIV protease enzyme. It helps control HIV infection by inhibiting or interfering with the protease enzyme that HIV needs to multiply.

KALETRA® is not a cure for HIV infection or AIDS. People taking KALETRA® may still develop infections or other serious illnesses associated with HIV disease and 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.

When it should not be used:

Do not take KALETRA® if you/your child:

- are allergic to lopinavir, ritonavir or to any of the non-medicinal ingredients in KALETRA®. (Refer to the subheading "**What the important non-medicinal ingredients are**" for a complete listing).
- are currently taking any of the following medicines, because they can cause serious problems or death if taken with KALETRA®:
  - ergotamine,dihydroergotamine (used to treat headaches), ergonovine, methylergonovine* (used after labor and delivery), such as Cafergot®, Migranal®, D.H.E. 45®, Ergotrate® Maleate*, Methergine™*, and others;
  - triazolam, midazolam - used to relieve anxiety and/or trouble sleeping;
  - astemizole* (e.g. Hismanal®), terfenadine* (e.g. Seldane®) - used to relieve allergy symptoms;
  - pimozide (e.g. Orap®) - used to treat schizophrenia;
  - cisapride* (e.g. Prepulsid®) - used to relieve certain stomach problems;
- are currently taking rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®. Rifampin may lower the amount of KALETRA® in your blood and make it less effective.
- are currently taking St. John's wort (*Hypericum perforatum*), a herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease KALETRA® levels and lead to increased viral load and possible resistance to KALETRA® or cross-resistance to other anti-HIV medicines.
- are currently taking the cholesterol-lowering medicines lovastatin (e.g. Mevacor®) or simvastatin (e.g. Zocor®) because of possible serious reactions. Talk to your doctor before you take any cholesterol-lowering medicines with KALETRA®.
- are currently taking the PDE5 Inhibitors vardenafil (Levitra®), use to treat erectile dysfunction, or sildenafil (Revatio®), used for the treatment of pulmonary arterial hypertension (PAH). These drugs may increase the risk of hypotension (low blood pressure), syncope (fainting), visual changes and prolonged erection.
- are currently taking salmeterol, also known as Advair® and Serevent®. Salmeterol may increase the risk of cardiovascular (heart) adverse events.

* **Products not marketed in Canada.**

- are currently taking any of these medications; your doctor may switch your medication.

What the medicinal ingredients are:

lopinavir and ritonavir

What the important non-medicinal ingredients are:

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

What dosage forms it comes in:

KALETRA® is available as an oral solution. Each mL of KALETRA® contains 80 mg of lopinavir and 20 mg of ritonavir.

KALETRA® is also available as film-coated tablets containing the following combinations of lopinavir and ritonavir: 100mg/25 mg; 200 mg/50 mg.

KALETRA® is also available as a soft gel capsule containing 133.3 mg of lopinavir and 33.3 mg of ritonavir.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Tell your doctor if you or your child develops symptoms such as:

- **nausea**
- **vomiting**
- **abdominal pain.**

These may be signs of problems with your pancreas (pancreatitis). Your doctor must decide if these are related to pancreatitis and what to do about them.

BEFORE you use KALETRA® talk to your doctor or pharmacist if:

- You/your child have liver problems or are infected with Hepatitis B or Hepatitis C
- You/your child have diabetes, or symptoms such as frequent urination, and/or increase in thirst
- You/your child have hemophilia. Patients taking KALETRA® may have increased bleeding
- You/your child are taking or planning to take other medicines, **including prescription, herbal and other medicines** you can buy without a prescription
- You have heart disease or heart condition, including conditions of Congenital Long QT Syndrome
- You have low potassium levels in your blood
- You are pregnant or breast-feeding. Pregnant or breast-feeding mothers should not take KALETRA® unless specifically directed by the doctor. Be sure to tell your doctor immediately if you are or may be pregnant or if you are breast-feeding a baby. It is recommended that HIV-infected women should not breast-feed their infants because of the possibility your baby can be infected with HIV through your breast milk
- You have hereditary fructose intolerance as this product contains fructose
- You have kidney problems or inability to metabolize propylene glycol as this medication contains propylene glycol
- You suffer from alcoholism, liver problems, epilepsy or brain injury, as this medication contains alcohol

- Changes in body fat have been seen in some patients taking antiretroviral therapy See **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**.

INTERACTIONS WITH THIS MEDICATION

KALETRA® may interact with certain other medications with possible clinical effects. The use of the following medicines together with KALETRA® should only take place on the basis of medical advice:

- medicines used to treat erectile dysfunction such as sildenafil (e.g. Viagra®) or tadalafil (e.g. Cialis®). Vardenafil (e.g. Levitra®) should not be taken with KALETRA®;
- medicines used to lower blood cholesterol such as rosuvastatin (e.g. Crestor®), atorvastatin (e.g. Lipitor®). Lovastatin (e.g. Mevacor®) or simvastatin (e.g. Zocor®) should not be taken with KALETRA®;
- some medicines affecting the immune system such as cyclosporin, sirolimus (e.g. Rapamune®) and tacrolimus;
- some medicines used to treat seasonal allergies and ear and eye infections such as dexamethasone and fluticasone propionate (e.g. Flonase®);
- contraceptives used to prevent pregnancy (e.g. ethinyl estradiol);
- medicines used to treat AIDS and related infections such as amprenavir* (e.g. Agenerase®), fosamprenavir (e.g. Telzir®), indinavir (e.g. Crixivan®), nelfinavir (e.g. Viracept®), saquinavir (e.g. Invirase®), didanosine (e.g. Videx®), tenofovir (e.g. Viread®) and rifabutin (e.g. Mycobutin®);
- medicines used to treat depression such as trazodone (e.g. Desyrel®), and bupropion (e.g. Wellbutrin® SR);
- certain heart medicines such as calcium channel antagonists including felodipine (e.g. Plendil®), nifedipine (e.g. Adalat®) and nicardipine* (e.g. Cardene®);
- medicines used to correct heart rhythm such as amiodarone (e.g. Cordarone®), flecainide (e.g. Tambocor®), bepridil* (e.g. Vascor®), systemic lidocaine, propafenone hydrochloride (e.g. Rythmol®), quinidine and digoxin;
- antifungals such as ketoconazole (e.g. Nizoral®), itraconazole (e.g. Sporanox®) and voriconazole (e.g. Vfend®);
- morphine-like medicines (e.g. methadone);
- anticonvulsants such as carbamazepine (e.g Tegretol®), phenytoin (e.g. Dilantin®) and phenobarbital;
- efavirenz (e.g. Sustiva™), nevirapine (e.g. Viramune®), amprenavir* (e.g. Agenerase®) or nelfinavir (e.g. Viracept®);
- warfarin and certain antibiotics such as rifabutin (e.g. Mycobutin®) and clarithromycin (e.g. Biaxin®);
- medicines used to treat cancer (e.g. vincristine, vinblastine).

*** Product not available in Canada.**

Patients taking KALETRA® should not take products containing St. John's Wort (*Hypericum perforatum*) as this may stop KALETRA® from working properly.

KALETRA® can be taken with acid reducing agents (such as omeprazole and ranitidine) with no dose adjustment.

PROPER USE OF THIS MEDICATION

It is important that you/your child take KALETRA® every day exactly as your doctor prescribed it. Even if you feel better, do not stop taking KALETRA® without talking to your doctor. Using

KALETRA® as recommended should give you the best chance to delay the development of resistance to the product.

It is therefore important that you remain under the supervision of your doctor while taking KALETRA®.

Usual dose:

The usual dose for adults is 5.0 mL of the oral solution twice a day (morning and night), in combination with other anti-HIV medicines. The doctor may prescribe KALETRA® as 10.0 mL of the oral solution once daily in combination with other anti-HIV medicines for some patients who have not taken anti-HIV medications in the past. KALETRA® should not be administered once daily in therapy experienced patients.

The dose for children from 6 months to 12 years of age will be determined by your doctor based on the child's height and weight. KALETRA® should not be administered once daily in pediatric patients less than 18 years of age.

Take KALETRA® oral solution with food to help it work better.

Overdose:

If you/your child realize you have taken more KALETRA® than you were supposed to, contact your doctor or local poison control centre right away. If you cannot reach your/your child's doctor, go to the hospital. Also, KALETRA® oral solution contains 42% alcohol and accidental ingestion could be toxic and potentially lethal to a young child.

Missed Dose:

If you/your child miss a dose of KALETRA®, it should be taken as soon as possible, and the next scheduled dose taken at its regular time. If it is almost time for your/your child's next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most commonly reported side effects of KALETRA® are abdominal pain, diarrhea (abnormal stool, and/or bowel movement), feeling weak or tired, headache, nausea, vomiting and rash.

- If you have liver disease such as Hepatitis B and Hepatitis C, taking KALETRA® may worsen your liver disease.
- Some patients have large increases in triglycerides and cholesterol (forms of fat that are found in your blood).
- Diabetes and high blood sugar (hyperglycemia) may occur in patients taking protease inhibitors such as KALETRA®. Symptoms of diabetes or high blood sugar may include frequent urination or increased thirst. Let your doctor know if you have or develop these symptoms while taking KALETRA®.
- Some patients with hemophilia have increased bleeding with protease inhibitors.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breasts, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Diarrhea	√		
	Rash	√		
	Headache	√		
	Nausea	√		
	Vomiting	√		
	tingling feeling in hands, feet and around lips	√		
Uncommon	chest pain		√	
	Pancreatitis		√	
	- abdominal pain		√	
	- nausea		√	
	- vomiting		√	

This is not a complete list of side effects. For any unexpected effects while taking KALETRA®, contact your doctor or pharmacist.

HOW TO STORE IT

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

KALETRA® oral solution should be stored at 2 to 8°C in a refrigerator. If you keep KALETRA® outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). Avoid exposure to excessive heat.

It is important to keep KALETRA® in the original package. Do not transfer to any other container.

Do not use after the expiry date stated on the pack.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at: www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678—6789
  - Mail to : Canada Vigilance Program
  Health Canada
  Postal Locator 0701C
  Ottawa, ON K1A 0K9

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