AUSTRALIAN PRODUCT INFORMATION – KALETRA®

(LOPINAVIR / RITONAVIR) TABLETS AND ORAL SOLUTION

1 NAME OF THE MEDICINE

Lopinavir / Ritonavir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Kaletra is a co-formulation of lopinavir and ritonavir.

Tablets

Kaletra tablets are available for oral administration in a strength of 200 mg of lopinavir and 50 mg of ritonavir with the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal anhydrous silica, and sodium stearylfumarate and the following inactive ingredients in the film coating: hypromellose, titanium dioxide, macrogol 400, hyprolose, talc, colloidal anhydrous silica, macrogol 3350, iron oxide red, and polysorbate 80.

Oral Solution

Kaletra Oral Solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per millilitre with the following ingredients: PEG-40 hydrogenated castor oil, purified water, sodium chloride, sodium citrate, saccharin sodium, acesulfame potassium, citric acid, absolute ethanol, propylene glycol, menthol, povidone, glycerol, high fructose maize syrup, peppermint oil, water, Magnasweet Flavour (2x) (ARTG No. 4333), Vanilla natural & artificial flavour (Yarnilla) 33869 (ARTG No. 4338) and Artificial cotton candy flavour (ARTG No. 4381).

Kaletra Oral Solution contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v).

3 PHARMACEUTICAL FORM

Kaletra is available as 200 mg lopinavir/50 mg ritonavir tablets. Kaletra 200/50 mg tablets are red, ovaloid, film-coated tablets debossed with the code ‘AL’ on one side.

Kaletra Oral Solution is a light yellow to golden coloured liquid, supplied in 60 mL amber-coloured multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL marked

dosing syringe (80 mg lopinavir/20 mg ritonavir per mL). Each pack contains five bottles of 60 mL.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Kaletra is indicated for the treatment of HIV-1 infection, in combination with other antiretroviral agents in adults and children aged 2 years and older. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts from controlled clinical studies (see 5.1 PHARMACODYNAMIC PROPERTIES).

4.2 Dose and method of administration

Tablets

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

Adults

The recommended dosage of Kaletra film coated tablets is 400/100 mg (two 200/50 mg tablets) twice daily. Kaletra tablets may also be administered as 800/200 mg (four 200/50 mg tablets) once daily, in patients with less than three lopinavir-associated mutations. There are insufficient data to support the use of once daily administration of Kaletra for adult patients with three or more lopinavir-associated mutations (See 5.1 PHARMACODYNAMIC PROPERTIES).

Concomitant Therapy: Efavirenz, Nevirapine, Amprenavir, or Nelfinavir

A dose increase of lopinavir/ritonavir to 500/125 mg twice daily (6.25 mL of oral solution) should be considered when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Paediatric Patients

The adult dose of Kaletra tablets (400/100 mg BD) may be used in children 35 kg or greater. Kaletra should not be administered once daily in paediatric patients.

Oral Solution

Adults

Kaletra oral solution is available to patients who cannot take a tablet formulation. The recommended dosage of Kaletra is 5 mL of oral solution (400/100 mg) twice daily taken with food. Kaletra oral solution may also be administered as 10 mL once daily with food, in patients with less than three lopinavir associated mutations.

Paediatric Patients

Total amounts of alcohol and propylene glycol from all medicines, including Kaletra Oral Solution, that are to be given to infants should be taken into account in order to avoid toxicity from these excipients (see 2 QUALITATIVE AND QUANTITATIVE COMPOSITION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and 4.9 OVERDOSE).

The recommended dosage for children 2 years and older is 230/57.5 mg/m^2 (or 12/3 mg/kg for children < 15 kg or 10/2.5 mg/kg for children ≥ 15kg) twice daily taken with food, up to a maximum dose of 400/100 mg (5 mL) twice daily. In subjects receiving concomitant nevirapine or efavirenz an increase in dosage to 300/75 mg/m^2 (or 13/3.25 mg/kg for children < 15 kg or 11/2.75 mg/kg for children ≥ 15 kg) twice daily taken with food, should be considered. Kaletra dosed once daily is not recommended for any paediatric patients.

The following tables contain dosing guidelines for Kaletra Oral Solution based on children weighing less than 40 kg.

Table 1: Paediatric Dosing Guidelines for Kaletra (80 mg lopinavir/20 mg ritonavir per mL) Oral Solution based on body weight without efavirenz, nevirapine or amprenavir

Weight (kg)	Dose (mg/kg)*	Volume of Oral Solution twice-daily (80 mg lopinavir/ 20 mg ritonavir per mL)	Administered Dose
7 to < 15 kg	12 mg/kg BD		
7 to 10 kg		1.25 mL	100/25 mg
> 10 to < 15 kg		1.75 mL	140/35 mg
15 to 40 kg	10 mg/kg BD		
15 to 20 kg		2.25 mL	180/45 mg

Table 1: Paediatric Dosing Guidelines for Kaletra (80 mg lopinavir/20 mg ritonavir per mL) Oral Solution based on body weight without efavirenz, nevirapine or amprenavir			
Weight (kg)	**Dose (mg/kg)***	**Volume of Oral Solution twice-daily (80 mg lopinavir/ 20 mg ritonavir per mL)**	**Administered Dose**
> 20 to 25 kg		2.75 mL	220/55 mg
> 25 to 30 kg		3.5 mL	280/70 mg
> 30 to 35 kg		4.0 mL	320/80 mg
> 35 to 40 kg		4.75 mL	380/95 mg
> 40 kg	See adult dosage recommendation		
* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).			

Table 2: Paediatric Dosing Guidelines for Kaletra (80 mg lopinavir/20 mg ritonavir per mL) Oral Solution based on body weight with efavirenz, nevirapine or amprenavir			
Weight (kg)	**Dose (mg/kg)***	**Volume of Oral Solution twice-daily (80 mg lopinavir/ 20 mg ritonavir per mL)**	**Administered Dose**
7 to < 15 kg	13 mg/kg BD		
7 to 10 kg		1.5 mL	120/30 mg
> 10 to < 15 kg		2.0 mL	160/40 mg
15 to 45 kg	11 mg/kg BD		
15 to 20 kg		2.5 mL	200/50 mg
> 20 to 25 kg		3.25 mL	260/65 mg
> 25 to 30 kg		4.0 mL	320/80 mg
> 30 to 35 kg		4.5 mL	360/90 mg
> 35 to 40 kg		5.0 mL	400/100 mg
> 40 kg	See adult dosage recommendation for concomitant therapy		
* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).			

4.3 Contraindications

Kaletra is contraindicated in patients with known hypersensitivity to lopinavir, ritonavir, or any excipients.

Kaletra should not be co-administered concurrently with drugs that are highly dependent on cytochrome 450 3A (CYP3A) for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 3.

Table 3: Drugs which should not be co-administered with Kaletra	
Drug Class	**Drug Within Class Not to Be Co-administered**
Alpha1-adrenoreceptor antagonist	Alfuzosin hydrochloride
Analgesic Sodium channel blocker	Suzetrigine
Antianginal	Ranolazine
Antiarrhythmic	Dronedarone
Antibiotics	Fusidic acid
Anticancer Agents	Neratinib, Apalutamide
Antigout	Colchicine in patients with renal and/or hepatic impairment
Antihistamines	Astemizole, terfenadine
Antipsychotics	Blonanserin, lurasidone, pimozide
Benzodiazepines	Midazolam, Triazolam
Ergot derivatives	Ergotamine, Dihydroergotamine, Ergometrine, Methylergometrine
GI motility agent	Cisapride
Herbal product	St John's Wort (*Hypericum perforatum)*
Hepatitis C direct acting antiviral	Elbasvir/grazoprevir
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin
Microsomal triglyceride transfer protein (MTTP) inhibitor	Lomitapide
Long acting beta-adrenoreceptor agonist	Salmeterol
PDE5 inhibitor	Sildenafil* only when used for the treatment of pulmonary arterial hypertension (PAH)
* See 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for co-administration of sildenafil in patients with erectile dysfunction	

Kaletra Oral Solution is contraindicated in children below the age of 2 years, pregnant women, patients with hepatic and renal failure and patients treated with disulfiram or metronidazole due to the potential risk of toxicity from the excipient propylene glycol.

4.4 Special warnings and precautions for use

Identified precautions

Diabetes Mellitus/Hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycaemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. Consideration should be given to the monitoring of blood glucose.

Pancreatitis

Pancreatitis has been observed in patients receiving Kaletra therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to Kaletra has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – 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.

Hepatic Impairment

Kaletra is principally metabolised by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function. 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 HCV co-infected patients with mild to moderate hepatic impairment (see 5.2 PHARMACOKINETIC PROPERTIES). Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further

transaminase elevations. 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 AST/ALT monitoring should be considered in these patients, especially during the first several months of Kaletra treatment.

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

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 protease inhibitors is under investigation (see 5.1 PHARMACODYNAMIC PROPERTIES).

Haemophilia

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. Neither a causal relationship or a mechanism of action between protease inhibitor therapy and these events has been established.

Fat Redistribution

Redistribution of body fat (fat loss or fat gain) has been associated with combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

QT Interval Prolongation

Post-marketing 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 hypokalaemia, and with other drugs that prolong the QT interval.

PR Interval Prolongation

Kaletra has been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Rare 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 or atazanavir) have been reported in patients receiving Kaletra. Kaletra should be used with caution in such patients.

Lipid Elevations

Treatment with Kaletra has resulted in increases in the concentration of total cholesterol and triglycerides (see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for additional information on potential drug interactions with Kaletra and HMG CoA reductase inhibitors.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including Kaletra. During the initial phase of combination antiretroviral treatment when the immune system responds, patients may develop an inflammatory response to asymptomatic or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyosistis, and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Use in the elderly

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.

Paediatric use

The safety and pharmacokinetic profiles of Kaletra in paediatric patients below the age of six months have not been established. For paediatric use of Kaletra Oral Solution, see 4.2 DOSE AND METHOD OF ADMINISTRATION. In HIV-infected patients aged six 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 paediatric patients in clinical trials is ongoing (see 5.1 PHARMACODYNAMIC PROPERTIES).

Effects on laboratory tests

Refer to 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) for laboratory abnormalities reported during clinical studies.

4.5 Interactions with other medicines and other forms of interactions

Kaletra is an inhibitor of CYP3A both *in-vitro* and *in-vivo*. Co-administration of Kaletra and drugs primarily metabolised 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. Agents that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in area-under-the-curve (AUC) (greater than 3-fold) when co-administered with Kaletra. Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in Table 3 under 4.3 CONTRAINDICATIONS.

Kaletra is metabolised by CYP3A. Co-administration of Kaletra and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see Table 4 below). Although not noted with concurrent ketoconazole, co-administration of Kaletra and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Kaletra has been shown *in-vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolised by cytochrome P450 enzymes and by glucuronidation.

Kaletra does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations. Kaletra has been shown to be a potent inducer of CYP2C19 activity. Interactions may exist upon co-administration of Kaletra and drugs primarily metabolised by CYP2C19.

These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with lopinavir/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

Anti-HIV Agents

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Stavudine and Lamivudine

No change in the pharmacokinetics of lopinavir was observed when Kaletra was given alone or in combination with stavudine and lamivudine.

Didanosine

For Kaletra tablets: It is recommended that didanosine be administered on an empty stomach; therefore, didanosine may be co-administered with Kaletra tablets without food.

For Kaletra 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.

Zidovudine and Abacavir

Kaletra induces glucuronidation, therefore Kaletra has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Tenofovir

A study has shown Kaletra increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving Kaletra and tenofovir should be monitored for tenofovir-associated adverse events.

All

Increased CPK, myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitors (PIs), particularly in combination with NRTIs.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine

No change in the pharmacokinetics of lopinavir was apparent in healthy adult subjects during nevirapine and Kaletra co-administration. Results from a study in HIV-positive paediatric subjects revealed a decrease in lopinavir concentrations during nevirapine co-administration (see Table 4 and 5 below). The effect of nevirapine in HIV-positive adults is expected to be similar to that in paediatric subjects and lopinavir concentrations may be decreased. The clinical significance of the pharmacokinetic interaction is unknown. Kaletra should not be administered once daily in combination with nevirapine.

Efavirenz

Increasing the dose of Kaletra tablets to 500/125 mg (given as two 200/50 mg tablets and one 100/25 mg tablet) twice daily co-administered with efavirenz 600 mg once daily resulted in similar lopinavir concentrations compared to Kaletra tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

Increasing the dose of Kaletra tablets to 600/150 (three 200/50 mg tablets) BD co-administered with efavirenz significantly increased the lopinavir plasma concentrations approximately 36% and ritonavir concentrations approximately 56% to 92% compared to Kaletra tablets 400/100 mg BD without efavirenz (see Table 4 and 5 below).

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.

Kaletra should not be administered once daily in combination with efavirenz.

Delavirdine

Delavirdine has the potential to increase plasma concentrations of lopinavir.

Rilpivirine

Concomitant use of lopinavir/ritonavir with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required. Refer to the rilpivirine product information.

Etravirine

Concomitant use of lopinavir/ritonavir with etravirine causes a decrease in the plasma concentrations of etravirine, but no dose adjustment is required. Refer to the etravirine product information.

Protease Inhibitors

Amprenavir

Kaletra is expected to increase concentrations of amprenavir (amprenavir 750 mg BD plus Kaletra produces increased AUC, similar maximum concentration (C_{max}), increased minimum concentration (C_{min}), relative to amprenavir 1200 mg BD). Co-administration of Kaletra and amprenavir result in decreased concentrations of lopinavir (see 4.2 DOSE AND METHOD OF ADMINISTRATION). Kaletra should not be administered once daily in combination with amprenavir.

Fosamprenavir

A study has shown that co-administration of Kaletra with fosamprenavir lowers amprenavir and lopinavir concentrations. Appropriate doses of the combination of fosamprenavir and Kaletra with respect to safety and efficacy have not been established. Kaletra should not be administered once daily in combination with fosamprenavir.

Indinavir

Kaletra is expected to increase concentrations of indinavir (indinavir 600 mg BD plus Kaletra produces similar AUC, decreased C_{max}, increased C_{min} relative to indinavir 800 mg TDS. The dose of indinavir may need to be decreased during co-administration with Kaletra 400/100 mg BD (see Table 5 below).

Nelfinavir

Kaletra is expected to increase concentrations of nelfinavir and increased M8 metabolite of nelfinavir (nelfinavir 1000 mg BD plus Kaletra produces similar AUC, similar C_{max}, increased C_{min} relative to nelfinavir 1250 mg BD). Co-administration of Kaletra and nelfinavir result in

decreased concentrations of lopinavir (see 4.2 DOSE AND METHOD OF ADMINISTRATION). Kaletra should not be administered once daily in combination with nelfinavir.

Ritonavir

When Kaletra was co-administered with an additional 100 mg ritonavir twice daily, lopinavir AUC increased 33% and C_{min} increased 64% as compared to Kaletra 400/100 mg (three soft gel capsules) twice daily (see Table 4).

Saquinavir

Kaletra is expected to increase concentrations of saquinavir (saquinavir 800 mg BD plus Kaletra produces increased AUC, increased C_{max}, increased C_{min} relative to saquinavir 1200 mg TDS). The dose of saquinavir may need to be decreased when co-administered with Kaletra 400/100 mg BD (see Table 5).

Tipranavir

In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, 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. The concomitant administration of lopinavir/ritonavir and tipranavir with low dose ritonavir is therefore not recommended.

<u>HIV CCR5 – antagonist</u>

Maraviroc

Concurrent administration of maraviroc with lopinavir/ritonavir will increase plasma levels of maraviroc. The dose of maraviroc should be decreased during co-administration with lopinavir/ritonavir 400/100 mg BD. For further details, see complete product information for maraviroc.

Hepatitis C antivirals

Telaprevir

Concomitant administration of telaprevir and lopinavir/ritonavir resulted in reduced telaprevir steady-state exposure, while the lopinavir steady state exposure was not affected.

Boceprevir

Concomitant administration of boceprevir and lopinavir/ritonavir resulted in reduced boceprevir and lopinavir steady-state exposure. It is not recommended to co-administer lopinavir/ritonavir and boceprevir.

Glecaprevir/Pibrentasvir

Concomitant administration of glecaprevir/pibrentasvir and lopinavir/ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.

Sofosbuvir/velpatasvir/voxilaprevir

Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and lopinavir/ritonavir is not recommended due to the potential for increased toxicity, which may negatively impact compliance.

Simeprevir

Concomitant use of lopinavir/ritonavir and simeprevir may result in increased plasma concentrations of simeprevir. It is not recommended to co-administer lopinavir/ritonavir and simeprevir.

Ombitasvir/paritaprevir/ritonavir and dasabuvir

Concentrations of ombitasvir, paritaprevir, and ritonavir may be increased when co-administered with lopinavir/ritonavir, therefore, co-administration is not recommended.

Other Drugs

Analgesic

Fentanyl

Kaletra inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with Kaletra.

Sodium Channel Blocker (suzetrigine [see 4.3 CONTRAINDICATIONS]): Co-administration of suzetrigine with a strong inhibitor of CYP3A may increase exposure of suzetrigine and its metabolite.

Antiarrhythmics (e.g. amiodarone, bepridil, dronedarone (see 4.3 CONTRAINDICATIONS), systemic lignocaine and quinidine).

Concentrations may be increased when co-administered with Kaletra. Caution is warranted and therapeutic concentration monitoring is recommended when available.

Digoxin

A literature report has shown that co-administration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when co-administering lopinavir/ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.

Anticancer Agents (e.g. abemaciclib, apalutamide, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vincristine, vinblastine)

Anticancer agents may have their serum concentrations increased when co-administered with Kaletra resulting in the potential for increased adverse events usually associated with these anticancer agents, some of which may be serious. Co-administration of venetoclax or ibrutinib with lopinavir/ritonavir could increase venetoclax or ibrutinib exposure potentially resulting in a serious risk of tumour lysis syndrome. Co-administration of encorafenib or ivosidenib with lopinavir/ritonavir could increase encorafenib or ivosidenib exposure potentially increasing the risk of serious adverse events such as QT interval prolongation. For venetoclax, encorafenib, ibrutinib, ivosidenib, nilotinib and dasatinib, refer to their product information for dosing instructions.

Co-administration of apalutamide is contraindicated with Kaletra since apalutamide may decrease exposure of Kaletra with potential loss of virologic response. In addition, co-administration of apalutamide and Kaletra may lead to increased exposure of apalutamide resulting in increased potential for adverse events including seizure.

Kinase Inhibitors (also see anticancer agents above)

Fostamatinib

Co-administration of fostamatinib with lopinavir/ritonavir could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia.

Anticoagulants

Warfarin

Concentrations of warfarin may be affected when co-administered with Kaletra. It is recommended that international normalised ratio be monitored.

Rivaroxaban

Co-administration of rivaroxaban and lopinavir/ritonavir may increase rivaroxaban exposure which may increase the risk of bleeding.

Antidepressants

Trazodone

Concomitant use of ritonavir and trazodone may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor such as lopinavir/ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Bupropion

Concurrent administration of bupropion with lopinavir/ritonavir will decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion).

Anticonvulsants

Phenobarbital, phenytoin, carbamazepine

These drugs are known to induce CYP3A4 and may decrease lopinavir concentrations. 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. Kaletra should not be administered once daily in combination with carbamazepine, phenobarbital or phenytoin.

Lamotrigine and valproate

Co-administration of lopinavir/ritonavir and either of these drugs was associated with reduction in exposure of the anticonvulsant. Use with caution. A dose increase of the anticonvulsant

may be needed when co-administered with lopinavir/ritonavir and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments.

Antifungals

Ketoconazole and itraconazole

Ketoconazole and itraconazole may have serum concentrations increased by Kaletra (see Table 4 and 5 below). High doses of ketoconazole and itraconazole (greater than 200 mg/day) are not recommended.

Voriconazole

Co-administration of voriconazole with Kaletra has not been studied. However, a study has shown that administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of Kaletra and voriconazole may result in decreased voriconazole concentrations and the potential for decreased voriconazole effectiveness and should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Otherwise, alternative antifungal therapies should be considered in these patients.

Antigout Agents

Concentrations of colchicine are expected to increase when co-administered with Kaletra. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see 4.3 CONTRAINDICATIONS). Refer to the colchicine product information for prescribing information.

Anti-infectives

Clarithromycin

Moderate increases in clarithromycin AUC are expected when co-administered with Kaletra. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered.

Antimycobacterial

Rifabutin

When rifabutin and Kaletra were co-administered for ten days, rifabutin (parent drug and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3.5- and 5.7-fold, respectively (see Table 4 and 5 below). On the basis of these data, a rifabutin dose reduction of 75% (i.e. 150 mg every other day or three times per week) is recommended when administered with Kaletra. Further dose reduction of rifabutin may be necessary.

Rifampicin

Due to large decreases in lopinavir concentrations, rifampicin should not be used in combination with standard dose Kaletra. The use of rifampicin with Kaletra, may lead to loss of virologic response and possible resistance to Kaletra or to the class of protease inhibitors or other co-administered antiretroviral agents.

In healthy volunteers, co-administration of rifampicin with 800/200 mg lopinavir/ritonavir BD resulted in decreases in lopinavir of up to 57%, and co-administration with lopinavir/ritonavir 400/400 mg BD resulted in decreases of up to 7% when compared to lopinavir/ritonavir 400/100 mg BD dosed in the absence of rifampicin (see Table 4 below). ALT and AST elevations have been noted in studies with doses of lopinavir/ritonavir greater than 400/100 mg BD co-administered with rifampicin and may be dependent on the sequence of dose administration.

The information with regard to the co-administration of Kaletra and rifampicin in the target population of TB-HIV co-infected patients is not available, and in the absence of such data, co-administration of rifampicin and Kaletra should be avoided. In case no alternatives are available, Kaletra should be initiated at standard doses for approximately 10 days prior to addition of rifampicin. Kaletra dose should then be titrated upward. Extreme caution and close monitoring of liver enzymes and plasma drug concentrations is warranted. (see Table 6 below for magnitude of interaction).

Bedaquiline

Co-administration of bedaquiline with strong CYP3A4 inhibitors may increase the systemic exposure of bedaquiline, which could potentially increase the risk of bedaquiline-related adverse reactions. Bedaquiline must be used cautiously with lopinavir/ritonavir, only if the benefit of co-administration outweighs the risk.

Delamanid

In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, exposures of delamanid and a delamanid metabolite, DM-6705, were slightly increased. Exposure to the delamanid metabolite has been associated with QTc prolongation.

Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended.

Anti-parasitics

Decreases in the therapeutic concentration of atovaquone are possible when co-administered with Kaletra. Increases in atovaquone doses may be necessary.

Antipsychotics

Caution should be exercised when lopinavir/ritonavir is co-administered with quetiapine. Due to CYP3A inhibition of lopinavir/ritonavir, concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities. When quetiapine is administered to patients who are receiving lopinavir/ritonavir, refer to the quetiapine product information for prescribing information.

Corticosteroids

Concomitant use of lopinavir/ritonavir and inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone, or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing’s syndrome and adrenal suppression. Concomitant use of lopinavir/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 lopinavir/ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide, or injectable triamcinolone.

Dexamethasone

Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations.

Fluticasone propionate

Consider alternatives to fluticasone propionate, particularly for long-term use.

Dihydropyridines Calcium Channel Blockers

Felodipine, nifedipine, nicardipine

May have their serum concentrations increased by Kaletra.

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, such as metronidazole.

PDE5 inhibitors

Co-administration of lopinavir/ritonavir with avanafil is not recommended, as it is expected to result in large increases in avanafil exposure.

Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil 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 increased associated adverse events such as hypotension, and prolonged erection.

Sildenafil

Use sildenafil for the treatment of erectile dysfunction 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 PAH patients (see 4.3 CONTRAINDICATIONS).

Tadalafil

Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events. When tadalafil is administered for the treatment of PAH to patients who are receiving Kaletra, refer to the tadalafil product information for prescribing information (see 4.3 CONTRAINDICATIONS).

Vardenafil

Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events (see 4.3 CONTRAINDICATIONS).

Herbal Products

Patients on Kaletra should not use products containing St John's Wort concomitantly, since this combination may be expected to result in reduced plasma concentrations of protease inhibitors. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance to lopinavir or to the therapeutic class of protease inhibitors (see 4.3 CONTRAINDICATIONS).

HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with Kaletra. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these drugs with Kaletra is contraindicated (see 4.3 CONTRAINDICATIONS).

Atorvastatin is less dependent on CYP3A for metabolism. When atorvastatin was given concurrently with Kaletra, a mean 4.7-fold and 5.9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with Kaletra, the lowest possible doses of atorvastatin should be administered. In a pharmacokinetic study, co-administration of rosuvastatin and Kaletra in healthy volunteers was associated with an approximately two and five fold increase in rosuvastatin steady state AUC (0 to 24) and C_{max}, respectively. Consideration should be given both to the benefit of lipid lowering by the use of rosuvastatin in patients receiving Kaletra and the potential risks of this increased exposure to rosuvastatin when initiating and up titrating rosuvastatin treatment. Results from a drug interaction study with Kaletra and pravastatin reveal no clinically significant interaction (see Table 4 and 5 below). The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with Kaletra. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Microsomal triglyceride transfer protein (MTTP) inhibitor

Lomitapide

Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27 fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated.

Immunosuppressants

Concentrations of these drugs (e.g. ciclosporin, tacrolimus and sirolimus (rapamycin)) may be increased when co-administered with Kaletra. More frequent therapeutic concentration monitoring is recommended until blood levels of these products have stabilised.

Methadone

Kaletra was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended (see Table 5 below).

Oral Contraceptives or Patch Contraceptives

Since levels of ethinyloestradiol may be decreased, alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives or patch contraceptives and Kaletra are co-administered (see Table 5 below).

Vasodilating Agents

Co-administration of bosentan and Kaletra increased steady-state bosentan C_{max} and AUC. Refer to the bosentan product information for prescribing information.

Gonadotropin releasing hormone (GnRH) receptor antagonist

Elagolix Co-administration of elagolix with lopinavir/ritonavir could increase elagolix exposure through inhibition of OATP, CYP3A, and P-gp. Known serious adverse events for elagolix include suicidal ideation and hepatic transaminase elevations. In addition, elagolix is a weak/moderate inducer of CYP3A, which may decrease exposure of lopinavir/ritonavir. Refer to the elagolix product information for dosing information with strong CYP-3A4 inhibitors

Clinically Significant Drug Interactions Are Not Expected

A drug interaction study has revealed no clinically significant interaction with Kaletra administered once or twice daily, and omeprazole or ranitidine (see Table 4 below).

Clinical studies showed no clinically significant interaction between lopinavir/ritonavir and raltegravir.

Based on known metabolic profiles, clinically significant drug interactions are not expected between Kaletra and desipramine (CYP2D6 probe), fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, or fluconazole in patients with normal renal and hepatic function.

Drug Interaction Studies

Drug interaction studies were performed with Kaletra and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of Kaletra on the AUC, C_{max} and C_{min} are summarised in Table 4 (effect of other drugs on lopinavir) and Table 5 (effect of Kaletra on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes.

Table 4: Drug Interactions
Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Kaletra (mg)	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	750 BD; 10 days	400/100 capsule BD; 21 days	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin	20 Daily; 4 days	400/100 capsule BD; 14 days	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz[1]	600 nocte; 9 days	400/100 capsule BD; 9 days	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 nocte; 9 days	500/125 tablet BD 10 days	19	1.12 (1.02 – 1.23)	1.06 (0.96 – 1.17)	0.9 (0.78 – 1.04)
	600 nocte; 9 days	600/150 tablet BD; 10 days	23	1.36 (1.28 - 1.44)	1.36 (1.28 - 1.44)	1.32 (1.21 - 1.44)
Ketoconazole	200 single dose	400/100 capsule BD; 16 days	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 BD, 10 days	400/100 capsule BD; 21 days	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 BD, steady-state (>1yr)[2]	400/100 capsule BD, steady-state (>1yr)	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)

Table 4: Drug Interactions
Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Kaletra (mg)	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
	7 mg/kg or 4 mg/kg Daily, 2 weeks; BD 1 week[3]	300/75 mg/m^2 oral solution BD; 3 weeks	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Omeprazole	40 Daily, 5 days	400/100 tablet BD; 10 days	11	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)
		800/200 tablet Daily; 10 days	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
Pravastatin	20 Daily; 4 days	400/100 capsule BD; 14 days	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 BD; 10 days	12	0.98 (0.95, 1.02)	0.98 (0.94, 1.01)	0.93 (0.89, 0.98)
		800/200 tablet Daily; 10 days	11	0.97 (0.95, 1.00)	0.95 (0.91, 0.99)	0.82 (0.74, 0.91)
Rifabutin	150 Daily; 10 days	400/100 capsule BD; 20 days	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampicin	600 Daily, 10 days	400/100 capsule BD; 20 days	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 Daily, 14 days	800/200 capsule BD; 9 days[4]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 Daily, 14 days	400/400 capsule BD; 9 days[5]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
					Co-administration of standard dose Kaletra and rifampicin is not recommended. (See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	
Ritonavir[2]	100 BD; 3 to 4 weeks	400/100 capsule BD; 3 to 4 weeks	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.
[2] Study conducted in HIV-positive adult subjects.
[3] Study conducted in HIV-positive paediatric subjects ranging in age from 6 months to 12 years.
[4] Titrated to 800/200 BD as 533/133 BD x 1 day, 667/167 BD x 1 day, then 800/200 BD x 7 days, compared to 400/100 BD x 10 days alone.
[5] Titrated to 400/400 BD as 400/200 BD x 1 day, 400/300 BD x 1 day, then 400/400 BD x 7 days, compared to 400/100 BD x 10 days alone.
* Parallel group design; n for Kaletra + co-administered drug, n for Kaletra alone

Table 5:	**Drug Interactions** **Pharmacokinetic Parameters for Co-administered Drug in the Presence of Kaletra (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for Recommended Alterations in Dose or Regimen)**					
Co-administered Drug	**Dose of Co-administered Drug (mg)**	**Dose of Kaletra (mg)**	**n**	**Ratio (with/without Kaletra) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00**		
				C_{max}	AUC	C_{min}
Amprenavir[1]	750 BD, 10 days combo vs. 1200 BD, 14 days alone	400/100 capsule BD, 21 days	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Atorvastatin	20 Daily; 4 days	400/100 capsule BD; 14 days	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 BD; 10 days	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	NA
Efavirenz	600 nocte; 9 days	400/100 capsule BD; 9 days	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Oestradiol	35 microgram Daily; 21 days (Brevinor-1®)	400/100 capsule BD; 14 days	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir[1]	600 BD, 10 days combo non-fasting vs. 800 TDS, 5 days alone fasting	400/100 capsule BD, 15 days	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 BD; 16 days	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	NA
Methadone	5 single dose	400/100 capsule BD; 10 days	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	NA
Nelfinavir[1] M8 metabolite	1000 BD, 10 days combo vs. 1250 BD, 14 days alone	400/100 capsule BD, 21 days	13	0.93 (0.82, 1.05) 2.36 (1.91, 2.91)	1.07 (0.95, 1.19) 3.46 (2.78, 4.31)	1.86 (1.57, 2.22) 7.49 (5.85, 9.58)
Nevirapine	200 Daily, 14 days; BD, 6 days	400/100 capsule BD; 20 days	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethisterone	1 Daily, 21 days (Brevinor-1®)	400/100 capsule BD; 14 days	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 Daily; 4 days	400/100 capsule BD; 14 days	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	NA

Table 5:	**Drug Interactions** **Pharmacokinetic Parameters for Co-administered Drug in the Presence of Kaletra (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for Recommended Alterations in Dose or Regimen)**					
Co-administered Drug	**Dose of Co-administered Drug (mg)**	**Dose of Kaletra (mg)**	**n**	**Ratio (with/without Kaletra) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00**		
				C_{max}	AUC	C_{min}
Rifabutin	150 Daily 10 days combo vs. 300 Daily, 10 days; alone	400/100 capsule BD, 10 days	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]	800 BD, 10 days combo vs. 1200 TDS, 5 days alone,	400/100 capsule BD, 15 days 400/100 capsule BD, 20 days	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
	1200 BD, 5 days combo vs. 1200 TDS 5 days alone		10	6.44 (5.59, 7.41)	9.91 (8.28, 11.86)	16.54 (10.91, 25.08)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] Ratio of parameters for amprenavir, indinavir, nelfinavir, and saquinavir are not normalised for dose.
[2] Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.
[3] Effect on the dose-normalised sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.
* Parallel group design; n for Kaletra + co-administered drug, n for co-administered drug alone.
NA = not available.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels up to 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.6-fold for lopinavir and 0.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BD).

Use in pregnancy

Pregnancy Category B3. No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and foetal development toxicities (early resorption, decreased foetal viability, decreased foetal

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 0.6-fold for lopinavir and 1.6-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BD). In a peri- and post-natal study in rats, a developmental toxicity (a decrease in survival of pups between birth and post-natal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and foetal developmental toxicity was 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 BD). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Kaletra should be used during pregnancy only if the potential benefits justify the potential risks to the foetus.

Use in lactation

It is not known whether lopinavir is secreted in human milk. Because of the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed when they are receiving Kaletra. Studies in rats showed that lopinavir is secreted in milk. In a peri- and post-natal study in rats, there was decreased survival of pups between birth and post-natal day 21 when dams were dosed at 40/20 mg/kg/day lopinavir/ritonavir and greater. Plasma drug levels were not measured in this study.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person’s ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (Undesirable effects)

Adults

Treatment-Emergent Adverse Events

Kaletra has been studied in over 2154 HIV-1 infected patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with Kaletra therapy was diarrhoea, which was generally of mild to moderate severity. Rates of

discontinuation of randomised therapy due to adverse events, including death, were 5.8% in Kaletra-treated and 4.9% in nelfinavir-treated patients in Study 863.

Treatment-Emergent clinical adverse events of moderate or severe intensity in greater than or equal to 2% of patients treated with combination therapy including Kaletra for up to 48 weeks (Studies 863, 418 and 730) and for up to 360 weeks (Study 720) are presented in Table 6 (antiretroviral -naïve patients) and for up to 48 weeks (Study 888 and 802), 84 weeks (Study 957) and 144 weeks (Study 765) in Table 7 (antiretroviral experienced patients). For other information regarding observed or potentially serious adverse events, please see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Table 6: Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

	Study 863 (48 Weeks)		**Study 418 (48 Weeks)**		**Study 720 (360 Weeks)**	**Study 730 (48 Weeks)**	
	LPV/r 400/100 mg BD + d4T + 3TC (N=326)	**Nelfinavir 750 mg TID + d4T + 3TC (N=327)**	**LPV/r Capsules 800/200 mg QD + TDF + FTC (N=115)**	**LPV/r Capsules 400/100 mg BD + TDF + FTC (N=75)**	**LPV/r BD[2] + d4T + 3TC (N=100)**	**LPV/r 800/200 mg QD + TDF +FTC (N=333)**	**LPV/r 400/100 mg BD + TDF +FTC (N=331)**
Gastrointestinal disorders							
Abdominal Distension	0.3%	0.6%	0.9%	0.0%	4.0%	0.3%	0.3%
Abdominal Pain	4.0%	3.1%	2.6%	2.7%	11.0%	0.6%	0.9%
Abnormal faeces	0.0%	0.3%	0.0%	0.0%	8.0%	0.0%	0.0%
Diarrhoea	15.6%	17.1%	15.7%	5.3%	28.0%	16.5%	15.1%
Dyspepsia	2.1%	0.3%	0.0%	1.3%	6.0%	0.0%	0.0%
Flatulence	1.5%	1.2%	1.7%	1.3%	4.0%	0.9%	0.6%
Nausea	6.7%	4.6%	8.7%	8.0%	16.0%	7.2%	5.4%

Table 6: Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients							
	Study 863 (48 Weeks)		**Study 418 (48 Weeks)**		**Study 720 (360 Weeks)**	**Study 730 (48 Weeks)**	
	LPV/r 400/100 mg BD + d4T + 3TC (N=326)	**Nelfinavir 750 mg TID + d4T + 3TC (N=327)**	**LPV/r Capsules 800/200 mg QD + TDF + FTC (N=115)**	**LPV/r Capsules 400/100 mg BD + TDF + FTC (N=75)**	**LPV/r BD[2] + d4T + 3TC (N=100)**	**LPV/r 800/200 mg QD + TDF +FTC (N=333)**	**LPV/r 400/100 mg BD + TDF +FTC (N=331)**
Vomiting	2.5%	2.4%	3.5%	4.0%	6.0%	3.3%	3.9%
General disorders and administration site conditions							
Asthenia	4.0%	3.4%	0.0%	0.0%	9.0%	0.3%	0.3%
Pain	0.6%	0.0%	0.0%	0.0%	3.0%	0.0%	0.0%
Nervous system disorders							
Headache	2.5%	1.8%	2.6%	2.7%	6.0%	1.5%	0.6%
Paraesthesia	0.9%	0.9%	0.0%	0.0%	2.0%	0.0%	0.0%
Psychiatric disorders							
Insomnia	1.5%	1.2%	0.0%	0.0%	3.0%	1.2%	0.0%
Libido decreased	0.3%	0.3%	0.0%	1.3%	2.0%	0.0%	0.3%
Depression	0.6%	1.5%	1.0%	0.0%	0.0%	0.0%	0.0%
Vascular disorders							
Vasodilatation	0.0%	0.0%	0.0%	0.0%	3.0%	0.0%	0.0%
Skin and subcutaneous disorders							
Rash	0.6%	1.5%	0.9%	0.0%	5.0%	0.3%	0.6%
Musculoskeletal and connective tissue disorder							
Myalgia	0.6%	0.9%	0.0%	0.0%	2.0%	0.0%	0.0%
Infections and infestations							
Bronchitis	0.0%	0.0%	0.0%	0.0%	2.0%	0.0%	0.3%
Endocrine disorders							
Hypogonadism male	0.0%	0.0%	0.0%	0.0%	2.1%	0.0%	0.0%
Metabolism and nutrition disorders							
Anorexia	0.9%	0.3%	0.9%	1.3%	2.0%	0.3%	0.9%

Table 6: Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients							
	Study 863 (48 Weeks)		**Study 418 (48 Weeks)**		**Study 720 (360 Weeks)**	**Study 730 (48 Weeks)**	
	LPV/r 400/100 mg BD + d4T + 3TC (N=326)	**Nelfinavir 750 mg TID + d4T + 3TC (N=327)**	**LPV/r Capsules 800/200 mg QD + TDF + FTC (N=115)**	**LPV/r Capsules 400/100 mg BD + TDF + FTC (N=75)**	**LPV/r BD[2] + d4T + 3TC (N=100)**	**LPV/r 800/200 mg QD + TDF +FTC (N=333)**	**LPV/r 400/100 mg BD + TDF +FTC (N=331)**
Investigations							
Weight Decreased	0.6%	0.3%	0.0%	0.0%	2.0%	0.0%	0.3%
Reproductive system and breast disorders							
Amenorrhoea	0.0%	0.0%	4.5%	0.0%	0.0%	0.0%	0.0%

[1] Includes adverse events of possible or probable relationship to study drug.

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

Definitions: d4T = Stavudine; 3TC = Lamivudine; TDF = Tenofovir; FTC = Emtricitabine; LPV = Lopinavir

Table 7: Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult antiretroviral-Experienced Patients					
	Study 888 (48 Weeks) (%)		**Study 957[2]and Study 765[3] (84-144 Weeks) (%)**	**Study 802 (48 Weeks)**	
	Kaletra 400/100 mg BD + NVP + NRTIs (n=148)	**Investigator-selected protease inhibitor(s) + NVP + NRTIs (n=140)**	**Kaletra BD + NNRTI + NRTIs (n= 127)**	**Kaletra 800/200 mg Once daily + NRTIs (n=300)**	**Kaletra 400/100 mg Twice daily +NRTIs (n=299)**

Table 7:	**Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult antiretroviral-Experienced Patients**				
Gastrointestinal disorders					
Abdominal pain	2.0%	2.1%	3.9%	2.0%	0.3%
Abdominal pain Upper	N/A	N/A	N/A	0.7%	2.0%
Abnormal faeces	0.0%	0.0%	2.4%	0.0%	0.0%
Diarrhoea	7.4%	9.3%	22.8%	14.0%	11.0%
Dysphagia	2.0%	0.7%	0.0%	0.0%	0.0%
Flatulence	0.7%	2.1%	1.6%	1.0%	1.0%
Nausea	6.8%	16.4%	4.7%	2.7%	7.4%
Vomiting	4.1%	12.1%	1.6%	2.0%	2.7%
General disorders and administration site conditions					
Asthenia	2.7%	6.4%	9.4%	0.3%	0.3%
Chills	2.0%	0.0%	0.0%	0.0%	0.0%
Pyrexia	2.0%	1.4%	1.6%	0.0%	0.3%
Pain	0.0%	0.0%	3.9%	0.0%	0.0%
Nervous system disorders					
Headache	2.0%	2.9%	2.4%	0.3%	0.0%
Paraesthesia	0.0%	1.4%	2.4%	0.0%	0.0%
Vascular disorders					
Hypertension	0.0%	0.0%	2.4%	0.0%	0.0%
Metabolism and nutrition disorders					
Anorexia	0.7%	2.9%	0.0%	0.0%	0.7%
Investigations					
Weight decreased	0.0%	1.4%	3.1%	0.3%	0.3%
Skin and subcutaneous disorders					
Rash	2.0%	1.4%	2.4%	0.0%	0.0%
Psychiatric disorders					
Insomnia	0.0%	2.1%	2.4%	0.0%	0.3%
Depression	0.7%	2.1%	3.1%	0.3%	0.0%

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

2 Includes adverse event data from patients receiving 400/100 mg BD (n=29) or 533/133 mg BD (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 BD (n=36) or 400/200 mg BD (n=34) for 144 weeks. Patients received Kaletra in combination with NRTIs and nevirapine.

Definitions: NVP = Nevirapine; NRTI = Nucleoside Reverse Transcriptase Inhibitors;
NNRTI = Nonnucleoside Reverse Transcriptase Inhibitors

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving Kaletra in all phase II/III 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.

Infections and infestations

Bacterial infection, bronchopneumonia, cellulitis, influenza, folliculitis, furunculosis, gastroenteritis, otitis media, perineal abscess, pharyngitis, rhinitis, sialadenitis, sinusitis and viral infection.

Neoplasms benign, malignant and unspecified

Benign neoplasm of skin, lipoma and neoplasm.

Blood and lymphatic system disorders

Anaemia, leukopenia, lymphadenopathy, neutropenia and splenomegaly.

Immune system disorders

Drug hypersensitivity, hypersensitivity, and immune reconstitution syndrome.

Endocrine disorders

Cushing's syndrome and hypothyroidism.

Metabolism and nutrition disorders

Dehydration, diabetes mellitus, hypertriglyceridaemia, hypercholesterolemia, weight decreased, decreased appetite, weight increased, increased appetite dyslipidaemia, hyperamylasaemia, hyperlipasaemia, hypovitaminosis, lactic acidosis, lipomatosis and obesity.

Psychiatric disorders

Abnormal dreams, affect lability, agitation, anxiety, apathy, confusional state, disorientation, mood swings, nervousness and thinking abnormal.

Nervous System disorders

Ageusia, amnesia, balance disorder, coordination abnormal, cerebral infarction, convulsion, dizziness, dysgeusia, dyskinesia, encephalopathy, extrapyramidal disorder, facial palsy, hypertonia, migraine, neuropathy, neuropathy peripheral, somnolence and tremor.

Eye disorders

Eye disorder and visual disturbance.

Ear and labyrinth disorders

Hyperacusis, tinnitus and vertigo.

Cardiac disorders

Angina pectoris, atrial fibrillation, atrioventricular block, myocardial infarction, palpitations and tricuspid valve incompetence.

Vascular disorders

Deep vein thrombosis, orthostatic hypotension, thrombophlebitis, varicose vein and vasculitis.

Respiratory, thoracic and mediastinal disorders

Asthma, cough, dyspnoea and pulmonary oedema.

Gastrointestinal disorders

Abdominal discomfort, abdominal pain lower, constipation, dry mouth, duodenitis enteritis, enterocolitis, entercolitis haemorrhagic, eructation, esophagitis, faecal incontinence, gastritis, gastric disorder, gastric ulcer, gastroesophageal reflux disease, haemorrhoids, mouth ulceration, pancreatitis, periodontitis, rectal haemorrhage, stomach discomfort and stomatitis.

Hepatobiliary disorders

Cholangitis, cholecystitis, cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly, jaundice and liver tenderness.

Skin and subcutaneous tissue disorders

Acne, alopecia, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, dry skin, eczema, hyperhidrosis, idiopathic capillaritis, nail disorder, pruritus, rash generalised, rash maculo-papular, seborrhoea, skin discoloration, skin hypertrophy, skin striae, skin ulcer and swelling face.

Musculoskeletal and connective tissue disorder

Arthralgia, arthropathy, back pain, muscular weakness, osteoarthritis, osteonecrosis and pain in extremity.

Renal and urinary disorders

Haematuria, nephritis, nephrolithiasis, renal disorder urine abnormality and urine odour abnormality.

Reproductive system disorders

Breast enlargement, ejaculation disorder, erectile dysfunction, gynaecomastia and menorrhagia.

General disorders and administration site conditions

Chest pain, cyst, drug interaction, oedema, oedema peripheral, face oedema, fatigue, hypertrophy and malaise.

Investigations

Drug level increased, glucose tolerance decreased and weight increased.

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy including Kaletra with Grade 3 to 4 laboratory abnormalities are presented in Table 8 and 9.

Table 8: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-naïve Patients

		Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	**Limit[1]**	**KALETRA 400/100 mg BD + d4T +3TC (N = 326)**	**Nelfinavir 750 mg TID + d4T + 3TC (N = 327)**	**KALETRA 800/200 mg QD + TDF + FTC (N = 115)**	**KALETRA 400/100 mg BD + TDF + FTC (N = 75)**	**KALETRA BD + d4T + 3TC (N = 100)**	**KALETRA QD + TDF +FTC (N=333)**	**KALETRA BD + TDF +FTC (N=331)**
Chemistry	**High**							
Glucose	> 250 mg/dL	2%	2%	3%	1%	4%	0%	<1%

Table 8: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-naïve Patients

		Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	**Limit[1]**	**KALETRA 400/100 mg BD + d4T +3TC (N = 326)**	**Nelfinavir 750 mg TID + d4T + 3TC (N = 327)**	**KALETRA 800/200 mg QD + TDF + FTC (N = 115)**	**KALETRA 400/100 mg BD + TDF + FTC (N = 75)**	**KALETRA BD + d4T + 3TC (N = 100)**	**KALETRA QD + TDF +FTC (N=333)**	**KALETRA BD + TDF +FTC (N=331)**
Uric Acid	> 12 mg/dL	2%	2%	0%	3%	5%	<1%	1%
SGOT/ AST[2]	> 180 U/L	2%	4%	5%	3%	10%	1%	2%
SGPT/ ALT[2]	> 215 U/L	4%	4%	4%	3%	11%	1%	1%
GGT	> 300 U/L	N/A	N/A	N/A	N/A	10%	N/A	N/A
Total Cholesterol	> 300 mg/dL	9%	5%	3%	3%	27%	4%	3%
Triglycerides	> 750 mg/dL	9%	1%	5%	4%	29%	3%	6%
Amylase	> 2 x ULN	3%	2%	7%	5%	4%	N/A	N/A
Lipase	> 2x ULN	NA	NA	NA	NA	NA	3%	5%
Chemistry	**Low**							
Calculated Creatinine Clearance	< 50 mL/min	NA	NA	NA	NA	NA	2%	2%
Haematology	**Low**							
Neutrophils	0.75 x 10^9/L	1%	3%	5%	1%	5%	2%	1%

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

Table 9: Grade 3 - 4 Laboratory Abnormalities Reported in ≥ 2% of Adult antiretroviral-Experienced Patients						
		Study 888 (48 Weeks) (%)		Study 957[2] and Study 765[3] (84-144 Weeks) (%)	Study 802 (48 weeks) (%)	
Variable	**Limit[1]**	**Kaletra 400/100 mg BD + NVP + NRTIs (n=148)**	**Investigator-selected protease inhibitor(s) + NVP + NRTIs (n=140)**	**Kaletra BD + NNRTI + NRTIs (n=127)**	**Kaletra 800/200mg Once daily + NRTIs (n=300)**	**Kaletra 400/100mg Twice daily +NRTIs (n=299)**
Chemistry	**High**					
Glucose	> 250 mg/dL	1	2	5	2	2
Total Bilirubin	> 3.48 mg/dL	1	3	1	1	1
SGOT/AST	> 180 U/L	5	11	8	3	2
SGPT/ALT	> 215 U/L	6	13	10	2	2
GGT	> 300 U/L	N/A	N/A	29	N/A	N/A
Total Cholesterol	> 300 mg/dL	20	21	39	6	7
Triglycerides	> 750 mg/dL	25	21	36	5	6
Amylase	> 2 x ULN	4	8	8	4	4
Lipase	> 2x ULN	N/A	N/A	N/A	4	1
Creatine Phosphokinase	> 4x ULN	N/A	N/A	N/A	4	5
Chemistry	**Low**					
Calculated Creatinine Clearance	< 50mL/min	N/A	N/A	N/A	3	3
Inorganic Phosphorus	< 1.5 mg/dL	1	0	2	1	< 1
Haematology	**Low**					
Neutrophils	0.75 x 10^9/L	1	2	4	3	4
Haemoglobin	< 80g/L	1	1	1	1	2

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

Paediatrics

Treatment-Emergent Adverse Events

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

Dysgeusia, vomiting, and diarrhoea were the most commonly reported drug related adverse events of any severity in paediatric patients treated with combination therapy including Kaletra for up to 48 weeks in Study 940. A total of 8 children experienced moderate or severe adverse events at least possibly related to Kaletra. Rash (reported in 3%) was the only drug-related clinical adverse event of moderate to severe intensity observed in greater than or equal to 2% of children enrolled.

Laboratory Abnormalities

The percentages of paediatric patients treated with combination therapy including Kaletra with Grade 3 to 4 laboratory abnormalities are presented in Table 10.

Table 10: Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% Paediatric Patients

Variable	Limit[+]	Kaletra BD + RTIs (n=100)
Chemistry	**High**	
Sodium	>149 mEq/L	3.0%
Total bilirubin	> 2.9 x ULN	3.0%
SGOT/AST	> 180 U/L	8.0%
SGPT/ALT	> 215 U/L	7.0%
Total Cholesterol	>300 mg/dL or > 7.77 mmol/L	3.0%
Amylase	> 2.5 x ULN	7.0%[++]
Chemistry	**Low**	
Sodium	< 130 mEq/L	3.0%
Hematology	**Low**	
Platelet Count	< 50 x 10^9/L	4.0%
Neutrophils	< 0.40 x 10^9/L	2.0%

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

Postmarketing Experience

Hepatobiliary disorders: Hepatitis has been reported in patients on Kaletra therapy.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme have been reported.

Cardiac disorders: Bradyarrhythmia has been reported.

Renal and urinary disorders: Nephrolithiasis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems

4.9 Overdose

Human experience of acute overdosage with Kaletra is limited. Treatment of overdose with Kaletra should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Kaletra. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Since Kaletra is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug. In cases of overdosage with Kaletra Oral Solution, consideration may be given to dialysis for removal of propylene glycol.

Kaletra Oral Solution contains 42.4% (v/v) alcohol. Accidental ingestion of the product by a young child could result in significant alcohol related toxicity.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Lopinavir, an inhibitor of the HIV-1 and HIV-2 proteases, prevents cleavage of the gag-pol polyprotein, resulting in the production of immature, non-infectious virus. As co-formulated in Kaletra, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of 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 microgram/mL, 1 microgram/mL equals 1.6 microM) and ranged from 4 to 11 nM (0.003 to 0.007 microgram/mL) against several HIV-1 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 microgram/mL), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance

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 in antiretroviral treatment naive patients has not yet been characterised. In a Phase III study of 653 antiretroviral treatment naive patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV greater than 400 copies/mL at week 24, 32, 40 and/or 48 were analysed. No evidence of genotypic or phenotypic resistance to Kaletra was observed in 37 evaluable Kaletra-treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to Kaletra in antiretroviral treatment naive paediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

Resistance to Kaletra has been noted to emerge in patients treated with other protease inhibitors prior to Kaletra therapy. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (greater than 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 protease inhibitor resistance immediately prior to

Kaletra therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognised to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on Kaletra therapy. The assessment of these mutational patterns is under study.

Cross-Resistance During Kaletra Therapy

Little information is available on the cross-resistance of viruses selected during therapy with Kaletra. Isolates from four patients previously treated with one or more protease inhibitors that developed increased lopinavir phenotypic resistance during Kaletra therapy either remained cross-resistant or developed cross-resistance to ritonavir, indinavir, and nelfinavir. All rebound viruses either remained fully sensitive or demonstrated modestly reduced susceptibility to amprenavir (up to 8.5-fold concurrent with 99-fold resistance to lopinavir). The rebound isolates from the two subjects with no prior saquinavir treatment remained fully sensitive to saquinavir.

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

Baseline mutations at codons L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/F/T, and I84V in HIV protease were found to be correlated with reduced virologic response to lopinavir. In lopinavir/ritonavir clinical database, the presence of protease mutations at positions 10, 20, 33, 36, 54 and 82 in the presence of multiple other protease mutations was statistically significantly associated with a lowered virologic response (HIV-1 RNA < 400 copies/mL within 12 months after administration of lopinavir/ritonavir) by logistic regression analysis. The presence of mutations at codons 47, 48 and 50 are also appeared to influence response, although the association was not statistically significant. Table 11 shows the 48-week virologic response (HIV RNA < 400 copies/mL) according to the number of the above protease inhibitor resistance mutations at baseline in studies M98-888 and M97-765 and study M98-957 (see below).

Table 11: 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]

No. of subjects with virologic response / total no. of subjects (%)			
Number of protease inhibitor mutations at baseline[1]	Study M98-888 (Single protease inhibitor-experienced[2], NNRTI-naïve) n = 130	Study M97-765 (Single protease inhibitor-experienced[3], NNRTI-naïve) n = 56	Study M98-957 (Multiple protease inhibitor-experienced[4], NNRTI-naïve) n = 50
0-2	76/103 (74%)	34/45 (76%)	19/20 (95%)
3-5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	n/a	1/4 (25%)

[1] Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L241, 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

Table 12 shows the 48-week virologic response (HIV-1 RNA < 50 copies/mL) in study 802 according to the number of lopinavir-associated resistance mutations listed in Table 13 present at baseline (see Clinical trials). There are insufficient data to support once daily administration of Kaletra for adult patients with three or more lopinavir-associated mutations.

Table 12: Virologic Response (HIV-1 RNA <50 copies/mL) at Week 48 by Baseline Number of Protease Substitutions Associated with Reduced Response to Kaletra[1]

Number of protease inhibitor substitutions at baseline[1]	Study 802 (Treatment experienced[2]) Kaletra Once Daily + NRTIs n=268	Study 802 (Treatment experienced[3]) Kaletra Twice Daily + NRTIs n=264
0-2	167/255 (65%)	154/250 (62%)
3-5	4/13 (31%)	8/14 (57%)
6 or more	N/A	N/A

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

[3] 81% NNRTI-experienced, 45% PI-experienced (20% nelfinavir, 17% indinavir, 13% atazanavir).

Clinical trials

Antiviral Activity of Kaletra in Patients With Previous Protease Inhibitor 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-naive patients with HIV RNA greater than 1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir, and ritonavir (Study M98-957). In this study, patients were initially randomised to receive one of two doses of Kaletra in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC_{50} values 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 greater than 4-fold reduced susceptibility to lopinavir. These 31 isolates had a mean reduction in lopinavir susceptibility of 27.9-fold.

After 48 weeks of treatment with Kaletra, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA less than or equal to 400 copies/mL was observed in 93% (25/27), 73% (11/15), and 25% (2/8) of patients with less than or equal to 10-fold, greater than 10 and less than 40-fold, and greater than or equal to 40-fold reduced susceptibility to lopinavir at baseline, respectively. Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic. Plasma HIV RNA less than or equal to 50 copies/mL was observed in 81% (22/27), 60% (9/15), and 25% (2/8) in the above groups of patients, 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.

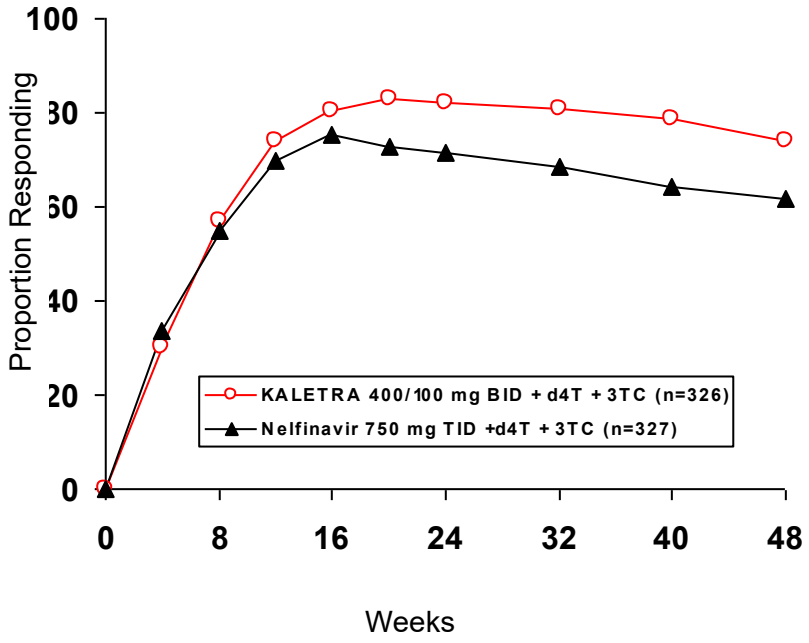
Patients Without Prior Antiretroviral Therapy

Study M98-863: Kaletra capsules BD + stavudine + lamivudine compared to nelfinavir TDS + stavudine + lamivudine.

Study M98-863 was a randomised, double-blind, multicentre trial comparing treatment with Kaletra capsules (400/100 mg BD) plus stavudine and lamivudine versus nelfinavir (750 mg TDS) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4 cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/mL (range: 2.6 to 6.8 log_{10} copies/mL).

Treatment response and outcomes of randomised treatment are presented in Figure 1 and Table 13, respectively.

Figure 1: Treatment Response Through 48 Weeks* (Study 863)



* Proportion of patients at each time point who have achieved and maintained HIV RNA less than 400 copies/mL, are on their original study medication, and have not experienced a new CDC Class C event.

Table 13: Outcomes of Randomised Treatment Through Week 48 (Study 863)		
Outcome	**Kaletra+d4T+3TC (n=326)**	**Nelfinavir+d4T+3TC (n=327)**
Responder*[1]	75%	62%
Virologic failure[2]	9%	25%
Rebound	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%

* Corresponds to rates at Week 48 in Figure 1.

[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. Overall discontinuation through week 48, including patients who discontinued subsequent to virologic failure, was 17% in the Kaletra arm and 24% in the nelfinavir arm.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the Kaletra arm compared to the nelfinavir arm with HIV 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 14.

Table 14: Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)						
Baseline Viral Load (HIV-1 RNA copies/mL)	**Kaletra +d4T+3TC**			**Nelfinavir +d4T+3TC**		
	<400 copies/mL[1]	**<50 copies/mL[2]**	**n**	**<400 copies/mL[1]**	**<50 copies/mL[2]**	**n**
<30,000	74%	71%	82	79%	72%	87
=30,000 to <100,00	81%	73%	79	67%	54%	79
=100,000 to <250,000	75%	64%	83	60%	47%	72
=250,000	72%	60%	82	44%	33%	89

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

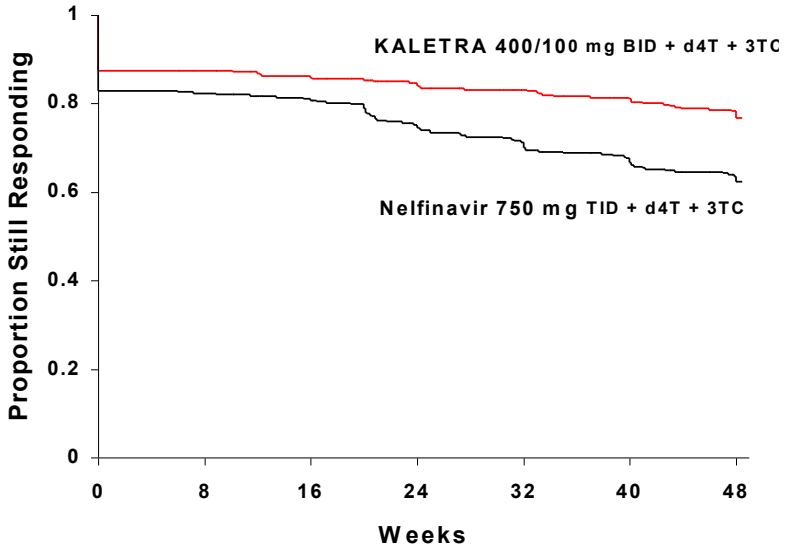
[2] Patients achieved HIV RNA <50 copies/mL at Week 48.

Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was 207 cells/mm^3 for the Kaletra arm and 195 cells/mm^3 for the nelfinavir arm.

Figure 2 displays the Kaplan-Meier estimates of the time to treatment failure in Study 863. The time of treatment failure was defined as the earliest time a patient experienced virologic failure

(two consecutive HIV RNA values demonstrating rebound above 400 copies/mL), a new CDC Class C event, or premature discontinuation from the study.

Figure 2: Time to Treatment Failure (Study 863)



Study M05-730: Kaletra 800/200mg Once Daily + tenofovir DF + emtricitabine compared to Kaletra 400/100mg BD + tenofovir DF + emtricitabine.

Study M05-730 was a randomised, open-label, multicentre 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 randomised 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 versus soft capsule). Patients were administered either the tablet or the soft capsule formulation for 8 weeks, after which all patients were administered the tablet formulation once daily or twice daily for the remainder of the study. Patients were administered emtricitabine 200 mg once daily and tenofovir DF 300 mg once daily. Mean age of patients enrolled was 39 years (range: 19 to 71); 75% were Caucasian, and 78% were male. Mean baseline CD4+ cell count was 216 cells/mm^3 (range: 20 to 775 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.0 log_{10} copies/mL (range: 1.7 to 7.0 log_{10} copies/mL).

Through 48 weeks of therapy, 78% in the Kaletra once-daily arm and 77% in the Kaletra twice-daily arm achieved and maintained HIV-1 RNA < 50 copies/mL (95% confidence interval for

the difference: -5.9% to 6.8%). Mean CD4+ cell count increases at Week 48 were 186 cells/mm^3 for the Kaletra once-daily arm and 198 cells/mm^3 for the Kaletra twice-daily arm.

Study M97-720: Kaletra capsules BD + stavudine + lamivudine

Study M97-720 is a randomised, blinded, multicentre trial evaluating treatment with Kaletra capsules at three dose levels (Group I: 200/100 mg BD and 400/100 mg BD; Group II: 400/100 mg BD and 400/200 mg BD) plus lamivudine (150 mg BD) and stavudine (40 mg BD) in 100 patients. All patients were converted to open label Kaletra at the 400/100 mg BD dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 70% were Caucasian, and 96% were male. Mean baseline CD4 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 in study 720, the proportion of patients with HIV RNA less than 400 (less than 50) copies/mL was 61% (59%) [n=100], and the corresponding mean increase in CD4 cell count was 501 cells/mm^3. Thirty-nine patients (39%) discontinued the study, including 15 (15%) discontinuations due to adverse events and 1 (1%) death. 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 RNA <400 copies/mL). Genotypic analysis of viral isolates was conducted on these patients and 10 additional patients with isolated HIV-1 RNA values > 400 copies/mL after week 24. Results were available from 19 patients and 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 phenotypic resistance.

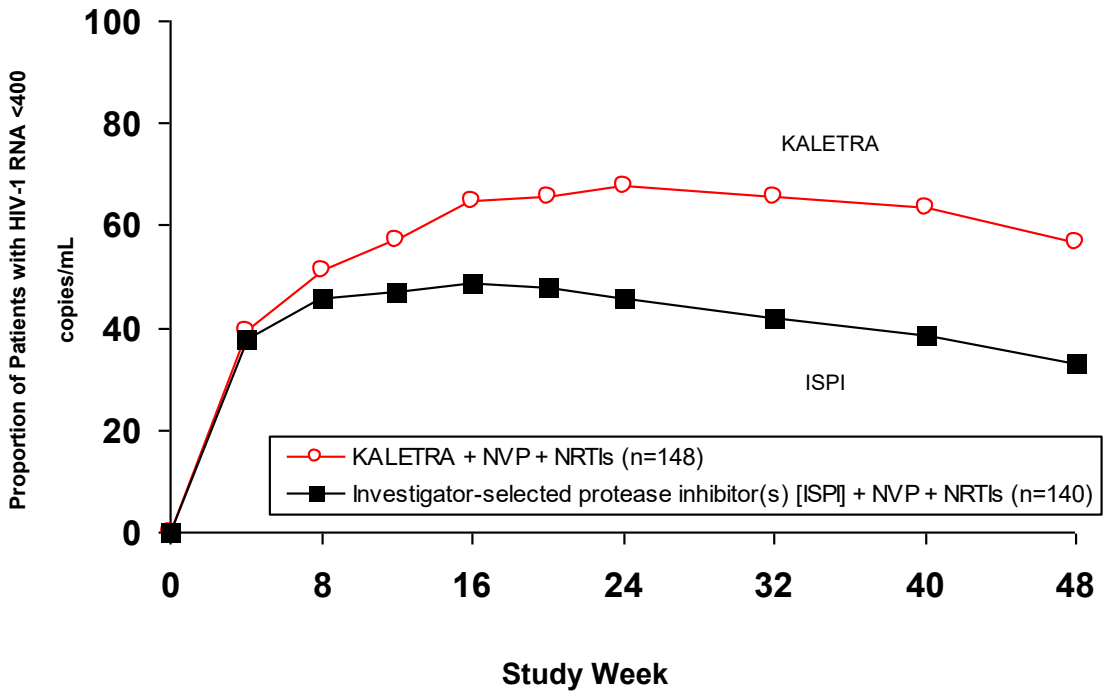
Patients with Prior Antiretroviral Therapy

Study M98-888: Kaletra capsules BD + nevirapine + NRTIs compared to investigator-selected protease inhibitor(s) + nevirapine + NRTIs

Study M98-888 is a randomised, open-label, multicentre trial comparing treatment with Kaletra capsules (400/100 mg BD) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and NRTIs in 288 single protease inhibitor-experienced, NNRTI-naive patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD4 cell count was 322 cells/mm^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 $\log_{10}$ copies/mL (range: 2.6 to 6.0 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomised treatment through Week 48 are presented in Figure 3 and Table 15 respectively.

Figure 3: Virologic Response Through Week 48, Study 888*†



* Roche AMPLICOR HIV-1 MONITOR Assay.

† Responders at each visit are patients who had achieved and maintained HIV-1 RNA <400 copies/mL without discontinuation by that visit.

Table 15: Outcomes of Randomised Treatment Through Week 48 (Study 888)

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

* Corresponds to rates at Week 48 in Figure 4.
[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.

Study M97-765: Kaletra capsules BD + nevirapine + NRTIs

Study M97-765 was a randomised, blinded, multicentre trial evaluating treatment with Kaletra capsules at two dose levels (400/100 mg BD and 400/200 mg BD) plus nevirapine (200 mg BD) and two NRTIs in 70 single protease inhibitor experienced, NNRTI naive patients. Patients had a mean age of 40 years (range 22 to 66), were 73% Caucasian, and were 90% male. Mean baseline CD4 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 765, the proportion of patients with HIV RNA less than 400 (less than 50) copies/mL was 54% (50%) [n=70], and the corresponding mean increase in CD4 cell count was 212 cells/mm^3. 27 patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

M06-802: Kaletra 800/200mg Once Daily + NRTIs compared to Kaletra 400/100mg BD + NRTIs in Antiretroviral-Experienced, HIV-1 infected patients.

This study was a randomised open-label study comparing the safety, tolerability, and antiviral activity of once daily and twice daily dosing of Kaletra tablets in 599 subjects with detectable viral loads while receiving their current antiviral therapy. Patients were randomised in a 1:1 ratio to receive either Kaletra 800/200 mg once daily (n = 300) or Kaletra 400/100 mg twice daily (n = 299). Patients were administered at least two nucleoside/nucleotide reverse transcriptase inhibitors selected by the investigator. Mean age of patients enrolled was 41 years (range: 21 to 73); 51% were Caucasian, and 66% were male. Mean baseline CD4+ cell count was 254 cells/mm^3 (range: 4 to 952 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.3 log_{10} copies/mL (range: 1.7 to 6.6 log_{10} copies/mL).

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

Table 16: Outcomes of Randomised Treatment Through Week 48 (Study 802)

Outcome	Kaletra Once Daily + NRTIs (n = 300)	Kaletra Twice Daily + NRTIs (n = 299)
Responder[1]	55%	52%
Virologic failure[2]	25%	28%
Rebound	12%	14%
Never suppressed through Week 48	13%	14%
Death	1%	1%

Table 16: Outcomes of Randomised Treatment Through Week 48 (Study 802)		
Outcome	**Kaletra Once Daily + NRTIs (n = 300)**	**Kaletra Twice Daily + NRTIs (n = 299)**
Discontinued due to adverse events	4%	6%
Discontinued for other reasons[3]	15%	14%
[1] Patients achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48.		
[2] Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48.		
[3] Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.		

Paediatric Use

Study M98-940

Study M98-940 was an open-label, multicentre trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of Kaletra Oral Solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive (44%) and experienced (56%) paediatric patients. All patients were NNRTI naive. Patients were randomised to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naive 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 five years (range six months to 12 years) with 14% less than two years. Mean baseline CD4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA less than 400 copies/mL was 80% for antiretroviral naive patients and 71% for antiretroviral-experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm^3 for antiretroviral naive and 284 cells/mm^3 for antiretroviral-experienced patients treated through 48 weeks. Premature discontinuations were noted in 2 (2%) subjects prior to week 48. One of these was considered by the investigator to be “unrelated” to study drug, the second “possibly” related to study drug.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 BD regimen without nevirapine and the 300/75 mg/m^2 BD regimen with

nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BD regimen (without nevirapine).

Once Daily Dosing

The pharmacokinetics of once daily Kaletra tablets have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Kaletra 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once daily regimen. Multiple dosing of 800/200 mg Kaletra once daily for 2 weeks without meal restriction (n=16) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 14.8 ± 3.5 microgram/mL, occurring approximately 6 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 5.4 microgram/mL. Lopinavir AUC over a 24 hour dosing interval averaged 206.5 ± 89.7 microgram·h/mL.

Effects on Electrocardiogram

QTcF interval was evaluated in a randomised, 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 400/100 mg twice-daily and supratherapeutic 800/200 mg twice-daily lopinavir/ritonavir, respectively. The two regimens resulted in exposures on Day 3 that were approximately 1.5 and 3-fold higher than those observed with recommended once-daily or twice-daily lopinavir/ritonavir 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.

Modest prolongation of the PR interval was also noted in subjects receiving lopinavir/ritonavir in the same study on Day 3. Maximum PR interval was 286 msec and no second or third degree heart block was observed (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

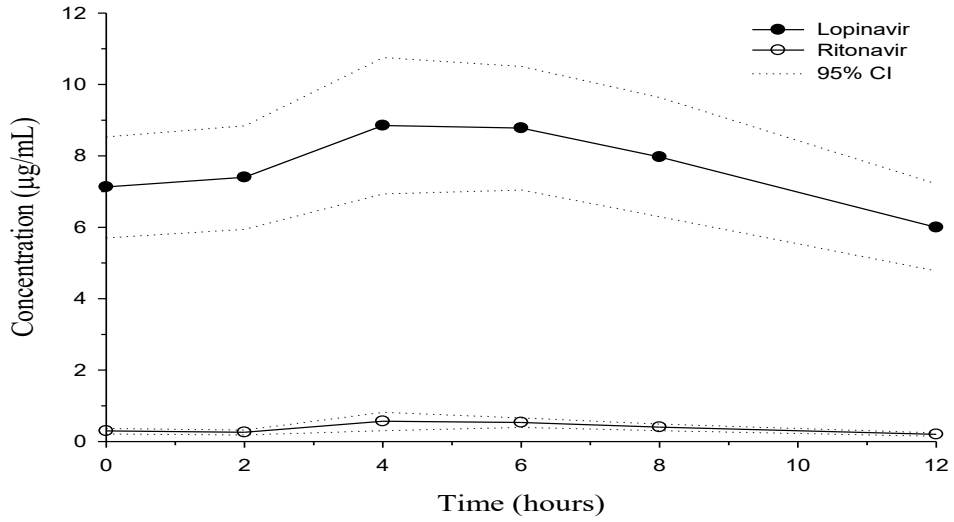
5.2 Pharmacokinetic properties

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 metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir.

Across studies, administration of Kaletra 400/100 mg BD 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 BD. The *in-vitro* antiviral EC50 of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Kaletra is due to lopinavir.

Figure 4 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after Kaletra 400/100 mg BD with food for three weeks from a pharmacokinetic study in HIV-infected adult subjects (n=19).

Figure 4: Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (n = 19)



Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg tablets are equal to or greater than those obtained with three 133/33 mg capsules under fed conditions with less pharmacokinetic variability.

Absorption

Multiple dosing with 400/100 mg Kaletra tablets twice daily for 2 weeks and without meal restriction produced a mean ± SD lopinavir C_{max} of 12.3 ± 5.4 microgram/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 microgram/mL. Lopinavir AUC over a 12 hour dosing interval averaged 113.2 ± 60.5 microgram•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of Food on Oral Absorption

Administration of a single 400/100 mg dose of Kaletra tablets under fed conditions (high-fat, 872 kcal, 56% from fat) compared to the fasted state was associated with no significant changes in C_{max} and AUC_{inf}, therefore, Kaletra tablets may be taken with or without food. Kaletra tablets have also shown less pharmacokinetic variability under all meal conditions compared to the Kaletra capsule.

Administration of Kaletra Oral Solution under non-fasting conditions, with a moderate fat meal (500-682 kcal, 22.7 to 25.1% calories from fat), lead to the mean increases of lopinavir AUC and C_{max} to 80 and 54% respectively. Relative to fasting, administration of Kaletra Oral Solution with a high fat meal (872 kcal, 55.8% from fat), increased lopinavir AUC and C_{max} by 130 and 56% respectively.

To enhance bioavailability and minimise 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 BD, and is similar between healthy volunteers and HIV-positive patients.

Metabolism

In-vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised 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, stabilising 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 faeces, respectively, after eight days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and faeces, 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).

Gender, Race and Age

Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Paediatric Patients

The pharmacokinetics of Kaletra 300/75 mg/m^2 BD and 230/57.5 mg/m^2 BD have been studied in a total of 53 paediatric patients, ranging in age from six months to 12 years. The 230/57.5 mg/m^2 BD regimen without nevirapine and the 300/75 mg/m^2 BD regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BD regimen (without nevirapine).

The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 microgram•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 microgram/mL, respectively after Kaletra 230/57.5 mg/m^2 BD without nevirapine (n=12), and were 85.8 ± 36.9 microgram•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5 microgram/mL, respectively after 300/75 mg/m^2 BD with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BD (six months to eight years) or 4 mg/kg BD (greater than eight years). Kaletra should not be administered once daily in paediatric patients.

Renal Impairment

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

Hepatic Impairment

Lopinavir is principally metabolised and eliminated by the liver. Multiple dosing of lopinavir/ritonavir 400/100 mg twice daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV–infected subjects with normal hepatic function. 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). Kaletra has not been studied in patients with severe hepatic impairment (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE- Hepatic Impairment).

5.3 Preclinical safety data

Genotoxicity

Neither lopinavir, ritonavir nor the drug combination was mutagenic or clastogenic in a series of assays for gene mutations (*S. typhimurium, E.coli* and mouse lymphoma cells *in-vitro*) and chromosomal damage (human lymphocytes *in-vitro* and mouse micronucleus assay *in-vivo*).

Carcinogenicity

Long-term carcinogenicity studies have been conducted with the lopinavir/ritonavir combination at oral doses of 20/10, 60/30 or 120/60 mg/kg/day in mice, and 10/5, 20/10 and 50/25 mg/kg/day in rats. The incidences of benign hepatocellular adenomas, and hepatocellular adenomas and carcinomas combined were significantly increased in high-dose male and female mice. The incidence of hepatocellular adenomas was increased in high-dose male rats. Lopinavir systemic exposures (AUCs) at the respective high-doses were approximately 2-fold (mice) and 0.5-fold (rats) the human exposure at the recommended therapeutic dose.

Carcinogenicity studies in mice and rats have been carried out with ritonavir alone. In male mice, at dietary levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both hepatocellular adenomas and adenomas and carcinomas combined. Based on AUCs, the exposure of males at the high dose was approximately 4-fold that of the exposure in humans with the recommended therapeutic dose (400/100mg Kaletra BD). In female mice there was a small increase in these tumours at the 200 mg/kg dose level. The exposure of females at the high dose was approximately 8-fold that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this

study, the exposure at the high dose was approximately 0.5-0.7 fold that of the exposure in humans with the 400/100mg Kaletra BD regimen.

The induction of liver tumours in mice by nongenotoxic mechanisms is generally considered to have limited relevance to human risk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refer to 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Tablets

Store below 25 °C.

Oral Solution

Store Kaletra Oral Solution at 2° to 8°C until dispensed. Refrigeration of Kaletra Oral Solution by the patients is not required if used within 42 days and stored below 25°C, however refrigeration by the patient is recommended whenever possible.

6.5 Nature and contents of container

Kaletra tablets are supplied in High Density Polyethylene (HDPE) bottles closed with propylene caps containing 120 Kaletra 200/50 mg tablets.

Kaletra Oral Solution is supplied in 60mL amber-coloured multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL marked dosing syringe (80 mg lopinavir/20 mg ritonavir per mL). Each pack contains five bottles of 60 mL.

6.6 Special precautions for disposal

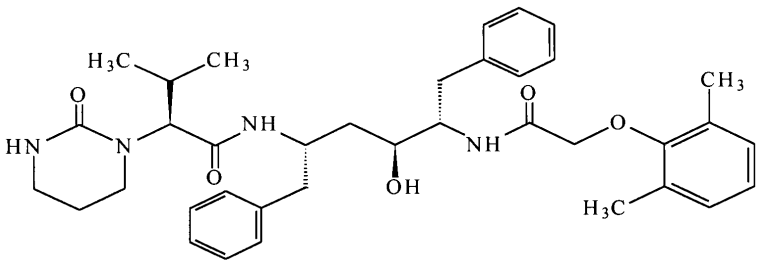
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical Structure

Lopinavir is chemically designated as [1S-[1R*,(R*), 3R*, 4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80.

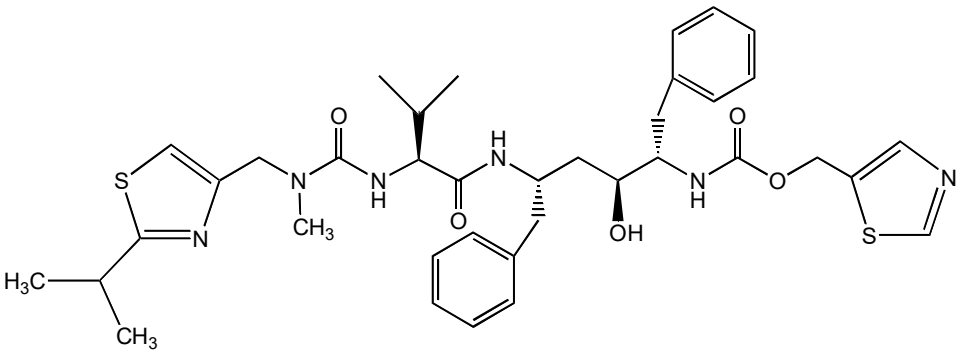
Lopinavir has the following structural formula:



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

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95.

Ritonavir has the following structural formula:



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

CAS number

Lopinavir: 192725-17-0

Ritonavir: 155213-67-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

10 September 2010

10 DATE OF REVISION

13 March 2026

Summary table of changes

Section Changed	Summary of new information
4.3	Addition of contraindication for concomitant use of lopinavir/ritonavir with suzetrigine.
4.5	Addition of suzetrigine drug-drug interaction with lopinavir/ritonavir.
4.5, 8.0, 10	Minor Editorial Updates