NEW ZEALAND DATA SHEET

1. PRODUCT NAME

KALETRA® 100 mg/25 mg film-coated tablets
KALETRA® 200 mg/50 mg film-coated tablets
KALETRA® 80 mg/20 mg per mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-Coated Tablets

Kaletra 100/25 mg: Each film-coated tablet contains 100 mg of lopinavir co-formulated with 25 mg of ritonavir as a pharmacokinetic enhancer.
Kaletra 200/50 mg: Each film-coated tablet contains 200 mg of lopinavir co-formulated with 50 mg of ritonavir as a pharmacokinetic enhancer.

Oral Solution

Kaletra 80/20 mg: Each 1 mL of oral solution contains 80 mg of lopinavir co-formulated with 20 mg of ritonavir as a pharmacokinetic enhancer.

Excipients with Known Effect

Kaletra oral solution contains alcohol (42.4% v/v), high fructose maize syrup, propylene glycol (15.3% w/v) (see section 4.3), Castor oil – PEG 40 hydrogenated and acesulfame potassium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-Coated Tablets

Kaletra 100/25 mg film-coated tablets are pale yellow, debossed with the Abbott logo and 'KC'.
Kaletra 200/50 mg tablets are yellow, ovaloid, film-coated tablets debossed with the Abbott logo and 'KA'.

Oral Solution

Kaletra oral solution is a light yellow to golden coloured liquid, supplied in 60 mL amber-coloured multiple-dose bottle containing 400 mg lopinavir and 100 mg ritonavir per 5 mL marked dosing syringe, equivalent to 80 mg lopinavir and 20 mg ritonavir per 1 mL of oral solution.

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 section 5.1 - Clinical Efficacy and Safety Results).

4.2 Dose and Method of Administration

Film-Coated 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 section 5.1, Table 10 and Table 11).

Concomitant Therapy: Efavirenz, Nevirapine, Amprenavir, or Nelfinavir

A dose increase of lopinavir/ritonavir to 500/125 mg twice daily (such as two 200/50 mg tablets and one 100/25 mg tablet or 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 section 4.5).

Paediatric Population (2 years of age and above)

The adult dose of Kaletra tablets (400/100 mg twice daily) may be used in children 35 kg or greater. For children weighing less than 35 kg and **able to swallow tablets**, refer to the dosing guideline tables below. Kaletra oral solution is available for children with a body weight of less than 7 kg. Kaletra once daily is not recommended for any paediatric patients.

The following table contains dosing guidelines for Kaletra 100/25 mg tablets in children based on body weight, without efavirenz, nevirapine, nelfinavir or amprenavir.

Table 1: Paediatric Dosing Guidelines without Concomitant Efavirenz, Nevirapine or Amprenavir		
Body Weight (kg)	**Recommended number of 100/25 mg Tablets Twice Daily**	**Administered Dose**
7 to < 10	1	100/25 mg
≥ 10 to < 25	2	200/50 mg
≥ 25 to < 35	3	300/75 mg
≥ 35	4	400/100 mg

Concomitant Therapy: Efavirenz, Nevirapine, Nelfinavir or Amprenavir

The following table contains dosing guidelines for Kaletra 100/25 mg tablets in children based on body weight, when used in combination with efavirenz, nevirapine, nelfinavir, or amprenavir.

Table 2: Paediatric Dosing Guidelines with Concomitant Efavirenz, Nevirapine or Amprenavir		
Body Weight (kg)	**Recommended number of 100/25 mg Tablets Twice Daily**	**Administered Dose**
≥ 10 to < 20	2	200/50 mg
≥ 20 to < 30	3	300/75 mg
> 30 kg to 45 kg	4	400/100 mg
> 45 kg	5	500/125 mg

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 Population (2 years of age and above)

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.

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 ≥ 15 kg) 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 should not be administered once daily in paediatric patients. The following tables contain dosing guidelines for Kaletra oral solution based on children weighing less than 40 kg.

Table 3: Paediatric Dosing Guidelines for Kaletra Oral Solution* based on Body Weight without Concomitant Efavirenz, Nevirapine or Amprenavir

Body Weight (kg)	Dose (mg/kg)*	Volume of Oral Solution Twice Daily*	Administered Dose
7 to < 15 kg	12 mg/kg twice daily		
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 twice daily		
15 to 20 kg		2.25 mL	180/45 mg
> 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 4: Paediatric Dosing Guidelines for Kaletra Oral Solution based on Body Weight with Concomitant Efavirenz, Nevirapine or Amprenavir

Body Weight (kg)	Dose (mg/kg)*	Volume of Oral Solution Twice Daily	Administered Dose
7 to < 15 kg	13 mg/kg twice daily		
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 twice daily		
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).

Use of Kaletra Oral Solution with a Feeding Tube

The prescribed dose of Kaletra oral solution can be administered via a feeding tube. Follow the instructions for the feeding tube to administer the medicine. Products containing alcohol, like Kaletra oral solution, are not recommended for use with polyurethane feeding tubes due to potential incompatibility.

4.3 Contraindications

Kaletra is contraindicated in patients with known hypersensitivity to lopinavir, ritonavir, or any excipients listed in section 6.1.

Kaletra should not be co-administered concurrently with medicines that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These medicines are listed in Table 5.

Table 5: Medicines which should not be co-administered with Kaletra

Therapeutic Class	**Medicines Within Class Not to Be Co-administered**
Alpha1-adrenoreceptor antagonist	alfuzosin hydrochloride
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
Lipid-modifying agents HMG-CoA reductase inhibitors Microsomal triglyceride transfer protein (MTTP) inhibitor	 lovastatin, simvastatin lomitapide

Long acting beta-adrenoreceptor agonist	salmeterol
PDE5 inhibitor	sildenafil * only when used for the treatment of pulmonary arterial hypertension (PAH)
* see sections 4.5 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

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 section 4.4 - 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 medicine 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 section 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.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as early as 7 days after the initiation of Kaletra in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with Kaletra therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of Kaletra treatment.

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 section 5.1 - Resistance).

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 nor a mechanism of action between protease inhibitor therapy and these events has 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 medicines 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 (see section 5.2 Pharmacokinetic properties).

Lipid Elevations

Treatment with Kaletra has resulted in increases in the concentration of total cholesterol and triglycerides (see section 4.8 Undesirable effects, Table 7 and 8). 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 section 4.5 - HMG-CoA Reductase Inhibitors for additional information on potential 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, polymyositis, 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.

Excipients in Kaletra Oral Solution

Healthcare professionals should be aware that Kaletra oral solution is highly concentrated and contains alcohol (42.4% v/v) and propylene glycol (and 15.3% w/v). Each 1 mL of Kaletra oral solution contains 356.3 mg of alcohol and 152.7 mg of propylene glycol, respectively.

Paediatric Population

The safety, efficacy and pharmacokinetic profiles of Kaletra in paediatric patients below the age of 14 days have not been established. For paediatric use of Kaletra oral solution, see sections 4.2 Dose and method of administration, and 4.9 Overdose. In HIV-infected patients aged 14 days to 18 years, the adverse event profile seen during clinical trials was similar to that for adult patients. Kaletra should not be administered once daily in paediatric patients.

Elderly Population

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 therapies.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Kaletra is an inhibitor of CYP3A (cytochrome P450 3A) both *in-vitro* and *in-vivo*. Co-administration of Kaletra and medicines 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 medicines 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 AUC (greater than 3-fold) when co-administered with Kaletra. Medicines that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in Table 5 under section 4.3 Contraindications.

Kaletra is metabolised by CYP3A. Co-administration of Kaletra and medicines that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see section 5.2 - Medicine Interactions). Although not noted with concurrent ketoconazole, co-administration of Kaletra and other medicines that inhibit CYP3A may increase lopinavir plasma concentrations.

These examples are a guide and not considered a comprehensive list of all possible medicines that may interact with Kaletra. 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 section 5.2 - Medicine Interactions, Tables 17 and 18). 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.

For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase of Kaletra should be considered when co-administered with nevirapine (see section 4.2 Dose and method of administration).

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 section 4.2 Dose and method of administration).

For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase of Kaletra should be considered when co-administered with efavirenz (see section 4.2 Dose and method of administration).

Increasing the dose of Kaletra tablets to 600/150 (three (3) tablets) twice daily 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 twice daily without efavirenz (see section 5.2 - Medicine Interactions, Tables 16 and 17).

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 Kaletra with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required. Refer to the rilpivirine prescribing information.

Etravirine

Concomitant use of Kaletra with etravirine causes a decrease in the plasma concentrations of etravirine, but no dose adjustment is required. Refer to the etravirine prescribing information.

Protease Inhibitors (PIs)

Amprenavir

Kaletra is expected to increase concentrations of amprenavir (amprenavir 750 mg twice daily plus Kaletra produces increased AUC, similar C_{max}, increased C_{min}, relative to amprenavir 1200 mg twice daily). Co-administration of Kaletra and amprenavir results in decreased concentrations of lopinavir. The dose of Kaletra may need to be increased when co-administered with amprenavir, particularly in patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir (see section 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.

Indinavir

Kaletra is expected to increase concentrations of indinavir (indinavir 600 mg twice daily plus Kaletra produces similar AUC, decreased C_{max}, increased C_{min} relative to indinavir 800 mg three times daily. The dose of indinavir may need to be decreased during co-administration with Kaletra 400/100 mg twice daily (see section 5.2 - Medicine Interactions, Table 17). Kaletra once daily has not been studied in combination with indinavir.

Nelfinavir

Kaletra is expected to increase concentrations of nelfinavir and increased M8 metabolite of nelfinavir (nelfinavir 1000 mg twice daily plus Kaletra produces similar AUC, similar C_{max}, increased C_{min} relative to nelfinavir 1250 mg twice daily). Co-administration of Kaletra and nelfinavir results in decreased concentrations of lopinavir. The dose of Kaletra may need to be increased when co-administered with nelfinavir, particularly in HIV patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir (see section 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 (3) soft gel capsules) twice daily (see section 5.2 - Medicine Interactions, Table 16).

Saquinavir

Kaletra is expected to increase concentrations of saquinavir (saquinavir 800 mg twice daily plus Kaletra produces increased AUC, increased C_{max}, increased C_{min} relative to saquinavir 1200 mg three times daily). The dose of saquinavir may need to be decreased when co-administered with Kaletra 400/100 mg twice daily (see section 5.2 - Medicine Interactions, Table 17). Kaletra once daily has not been studied in combination with saquinavir.

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 Kaletra (400/100 mg twice daily), resulted in a 55% and 70% reduction in lopinavir AUC and C_{min}, respectively. The concomitant administration of Kaletra and tipranavir with low dose ritonavir is therefore not recommended.

Hepatic C direct acting antivirals

Boceprevir

Concomitant administration of boceprevir and Kaletra resulted in reduced boceprevir and lopinavir steady-state exposure (see section 5.2 - Medicine Interactions, Tables 17 and 18). It is not recommended to co-administer Kaletra and boceprevir.

Glecaprevir/pibrentasvir

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

Ombitasvir/paritaprevir/ritonavir and dasabuvir

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

Simeprevir

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

Sofosbuvir/velpatasvir/voxilaprevir

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

Telaprevir

Concomitant administration of telaprevir and Kaletra resulted in reduced telaprevir steady-state exposure, while the lopinavir steady state exposure was not affected (see section 5.2 - Medicine Interactions, Tables 17 and 18).

HIV CCR5 – antagonist

Maraviroc

Concurrent administration of maraviroc with Kaletra will increase plasma levels of maraviroc (see section 5.2 - Medicine Interactions, Table 17). The dose of maraviroc should be decreased during co-administration with Kaletra 400/100 mg twice daily. For further details, see complete prescribing information for maraviroc.

Other Drugs

Analgesics

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.

Antiarrhythmics (amiodarone, bepridil, dronedarone (see section 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 Kaletra with digoxin, with appropriate monitoring of serum digoxin levels.

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

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 Kaletra could increase venetoclax or ibrutinib exposure, potentially resulting in a serious risk of tumor lysis syndrome. Coadministration of encorafenib or ivosidenib with Kaletra 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 prescribing information for dosing instructions. Coadministration of apalutamide is contraindicated with Kaletra, since apalutamide may decrease exposure of Kaletra, with potential loss of virologic response. In addition, coadministration of apalutamide and Kaletra may lead to increased exposure of apalutamide, resulting in increased potential for adverse events, including seizure.

Anticoagulants

Warfarin

Concentrations may be affected when co-administered with Kaletra. It is recommended that INR (international normalised ratio) be monitored.

Rivaroxaban

Coadministration of rivaroxaban and Kaletra may increase rivaroxaban exposure, which may increase the risk of bleeding.

Anticonvulsants

Phenobarbital, phenytoin, carbamazepine

These drugs are known to induce CYP3A4 and may decrease lopinavir concentrations. Kaletra should not be administered once daily in combination with carbamazepine, phenobarbital or phenytoin. In addition, co-administration of phenytoin and Kaletra resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with Kaletra.

Lamotrigine and valproate

Co-administration of Kaletra and either of these medicines was associated with reduction in exposure of the anticonvulsant; 50% reduction in lamotrigine exposure has been reported. Use with caution. A dose increase of the anticonvulsant may be needed when co-administered with Kaletra and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments (see section 5.2 - Medicine Interactions, Table 17).

Antidepressants

Bupropion

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

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 Kaletra, the combination should be used with caution and a lower dose of trazodone should be considered.

Antifungals

Ketoconazole and itraconazole

Either of these medicines may have serum concentrations increased by Kaletra (see section 5.2 - Medicine Interactions, Tables 17 and 18). High doses of ketoconazole and itraconazole (greater than 200 mg/day) are not recommended.

Voriconazole

A study has shown that co-administration of ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of Kaletra and voriconazole should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Antigout Agents

Colchicine

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 section 4.3 Contraindications). Refer to the colchicine product information for prescribing information.

Anti-infective

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.

Anti-mycobacterial

Rifabutin

When rifabutin and Kaletra were co-administered for ten days, rifabutin (parent active substance and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3.5- and 5.7-fold, respectively (see section 5.2 - Medicine Interactions, Tables 17 and 18). 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 standard dose 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.

Co-administration of rifampicin with 800/200 mg Kaletra twice daily resulted in decreases in lopinavir of up to 57%, and co-administration with Kaletra 400/400 mg twice daily resulted in decreases of up to 7% when compared to Kaletra 400/100 mg twice daily dosed in the absence of rifampicin (see section 5.2 - Medicine Interactions, Table 16).

ALT and AST elevations have been noted in studies with higher doses of lopinavir/ritonavir co-administered with rifampicin, and may be dependent on the sequence of dose administration. If co-administration is being considered, Kaletra should be initiated at standard doses for approximately 10 days prior to addition of rifampicin. The Kaletra dose should then be titrated upwards. Close monitoring of liver function is indicated.

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. In a healthy volunteer drug interaction study of 400 mg single dose bedaquiline and Kaletra 400/100 mg twice daily for 24 days, bedaquiline exposures (AUC) were increased by 22%. Bedaquiline must be used cautiously with Kaletra, 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 Kaletra 400/100 mg twice daily for 14 days, exposures of delamanid and a delamanid metabolite, DM-6705, were slightly increased. Due to the risk of QTc prolongation associated with exposure to DM-6705, if co-administration of delamanid with Kaletra is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended.

Anti-parasitic

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

Anti-psychotics

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

Corticosteroids

Concomitant use of Kaletra 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 Kaletra 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 Kaletra has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide, or injectable triamcinolone. Consider alternatives to fluticasone propionate, budesonide, and injectable triamcinolone, particularly for long-term use.

Dexamethasone

Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations.

Fluticasone propionate

Concomitant use of Kaletra and fluticasone 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.

Dihydropyridines Calcium Channel Blockers

Medicines such as felodipine, nifedipine and 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

Particular caution should be used when prescribing avanafil, 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.

Avanafil

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

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 pulmonary arterial hypertension (PAH) patients (see section 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 pulmonary arterial hypertension to patients who are receiving Kaletra, refer to the tadalafil product information for prescribing information.

Vardenafil

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

GnRH Receptor Antagonists

Elagolix

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

Kinase Inhibitors (see also anticancer agents, above)

Fostamatinib

Coadministration of fostamatinib with Kaletra could increase fostamatinib metabolite R406 exposure, resulting in dose-related adverse events, such as hepatotoxicity and neutropenia.

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 lopinavir/ritonavir. 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 section 4.3 Contraindications).

HMG-CoA Reductase Inhibitors

Lovastatin and simvastatin

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, concomitant use of Kaletra with lovastatin or simvastatin is contraindicated (see section 4.3 Contraindications).

Atorvastatin, fluvastatin, pravastatin and rosuvastatin

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.

Caution should be exercised if HIV protease inhibitors, including Kaletra, are used concurrently with rosuvastatin or with other HMG-CoA reductase inhibitors that are metabolised by the CYP3A4 pathway (e.g. atorvastatin), as this may increase the potential for serious reactions such as myopathy, including rhabdomyolysis.

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. Results from a drug interaction study with Kaletra and pravastatin reveal no clinically significant interaction (see section 5.2 - Medicine Interactions, Tables 17 and 18).

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 (see section 4.3 Contraindications).

Immunosuppressants

Concentrations of these drugs (e.g. cyclosporin, 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 section 5.2 - Medicine Interactions, Table 17).

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 section 5.2 - Medicine Interactions, Table 17).

Vasodilating Agents

Bosentan

Co-administration of bosentan and Kaletra increased steady-state bosentan maximum concentrations (C_{max}) and area-under-the-curve (AUC) by 6-fold and 5-fold, respectively. Refer to the bosentan product information for prescribing information.

Clinically Significant Drug Interactions Are Not Expected

Drug interaction studies reveal no clinically significant interaction with Kaletra administered with desipramine (CYP2D6 probe), omeprazole or ranitidine (see section 5.2 - Medicine Interactions, Table 16).

Clinical studies showed no clinically significant interaction between Kaletra and raltegravir.

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

4.6 Fertility, Pregnancy and Lactation

Fertility

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at maximum achievable doses producing drug exposures which were comparable to or slightly less than those achieved with the recommended therapeutic dose levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily).

Pregnancy (Category B3)

Kaletra oral solution is contraindicated in pregnant women, due to the potential risk of toxicity from the excipient propylene glycol (see section 4.3 Contraindications).

Risk Summary

Lopinavir/ritonavir has been evaluated in 3,366 women during pregnancy. Available human data suggest that lopinavir/ritonavir does not increase the risk of overall major birth defects compared to the background rate. Lopinavir/ritonavir can be used during pregnancy if clinically needed.

Antiretroviral Pregnancy Registry

In post-marketing surveillance through the Antiretroviral Pregnancy Registry, established since January 1989, no increased risk of birth defects has been reported among over 1,000 women exposed to

lopinavir/ritonavir in the first trimester. The prevalence of birth defects after any trimester exposure to lopinavir is comparable to the prevalence observed in the general population. No pattern of birth defects suggestive of a common aetiology was seen.

Clinical Trials

In an open-label pharmacokinetic study, 12 HIV-infected pregnant women who were less than 20 weeks of gestation and on combination antiretroviral therapy initially received lopinavir/ritonavir 400 mg/100 mg (two 200/50 mg tablets) twice daily up to a gestational age of 30 weeks. At 30 weeks age of gestation, the dose was increased to 500/125 mg (two 200/50 mg tablets plus one 100/25 mg tablet) twice daily until subjects were 2 weeks postpartum. Except for two reported TEAEs (anaemia in a zidovudine and penicillin-treated patient, and H1N1 influenza), no other serious adverse events and deaths were reported. All subjects tolerated the dose increase, with no premature discontinuations.

In another open-label pharmacokinetic study, 19 HIV-infected pregnant women received lopinavir/ritonavir 400/100 mg twice daily as part of combination antiretroviral therapy during pregnancy from before conception. Laboratory abnormalities included 2 cases of Grade 3 increases in ALT. Pregnancy related events included 1 case of pre-eclampsia, 6 preterm deliveries, 7 cases of low birth weight infants (<2,500 grams), and 2 stillbirths. No deaths, serious adverse events or discontinuations due to adverse events were reported. Seventeen of 19 patients had HIV RNA < 50 copies/mL at delivery.

No treatment-related malformations were observed when lopinavir/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 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily). In a perinatal and postnatal study in rats, a developmental toxicity (a decrease in survival of pups between birth and postnatal 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 twice daily).

Lactation

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. It is not known whether lopinavir is secreted in human milk.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be informed that nausea has been reported during treatment with Kaletra (see section 4.8 Undesirable effects).

Kaletra oral solution contains approximately 42% v/v alcohol.

4.8 Undesirable Effects

Adults

Treatment-Emergent Adverse Events

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

Commonly reported adverse reactions to lopinavir/ritonavir included diarrhoea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. Diarrhoea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridemia and hypercholesterolemia may occur later. The following have been identified as adverse reactions of moderate or severe intensity (Table 6):

Table 6: Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult Patients Receiving lopinavir/ritonavir in Combined Phase II/IV Studies (N=2,612)		
System Organ Class (SOC) and Adverse Reaction	**n**	**%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
anaemia*	54	2.067
leukopenia and neutropenia*	44	1.685
lymphadenopathy*	35	1.340
CARDIAC DISORDERS		
atherosclerosis such as myocardial infarction*	10	0.383
atrioventricular block*	3	0.115
tricuspid valve incompetence*	3	0.115
EAR AND LABYRINTH DISORDERS		
vertigo*	7	0.268
tinnitus	6	0.230
ENDOCRINE DISORDERS		
hypogonadism*	16	0.785[1]
EYE DISORDERS		
visual impairment*	8	0.306
GASTROINTESTINAL DISORDERS		
diarrhoea*	510	19.525
nausea	269	10.299
vomiting*	177	6.776
abdominal pain (upper and lower)*	160	6.126
gastroenteritis and colitis*	66	2.527
dyspepsia	53	2.029
pancreatitis*	45	1.723
Gastroesophageal Reflux Disease (GORD)*	40	1.531
haemorrhoids	39	1.493
flatulence	36	1.378
abdominal distension	34	1.302
constipation*	26	0.995
stomatitis and oral ulcers*	24	0.919
duodenitis and gastritis*	20	0.766

gastrointestinal haemorrhage including rectal haemorrhage*	13	0.498
dry mouth	9	0.345
gastrointestinal ulcer*	6	0.230
faecal incontinence	5	0.191
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
fatigue including asthenia*	198	7.580
HEPATOBILIARY DISORDERS		
hepatitis including AST, ALT, and GGT increases*	91	3.484
hepatomegaly	5	0.191
cholangitis	3	0.115
hepatic steatosis	3	0.115
IMMUNE SYSTEM DISORDERS		
hypersensitivity including urticaria and angioedema*	70	2.680
immune reconstitution syndrome	3	0.115
INFECTIONS AND INFESTATIONS		
upper respiratory tract infection*	363	13.897
lower respiratory tract infection*	202	7.734
skin infections including cellulitis, folliculitis, and furuncle*	86	3.292
METABOLISM AND NUTRITION DISORDERS		
hypercholesterolemia*	192	7.351
hypertriglyceridemia*	161	6.164
weight decreased*	61	2.335
decreased appetite	52	1.991
blood glucose disorders including diabetes mellitus*	30	1.149
weight increased*	20	0.766
lactic acidosis*	11	0.421
increased appetite	5	0.191
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
musculoskeletal pain including arthralgia and back pain*	166	6.355
myalgia*	46	1.761
muscle disorders such as weakness and spasms*	34	1.302
rhabdomyolysis*	18	0.689
osteonecrosis	3	0.115

NERVOUS SYSTEM DISORDERS		
headache including migraine*	165	6.317
insomnia*	99	3.790
neuropathy and peripheral neuropathy*	51	1.953
dizziness*	45	1.723
ageusia*	19	0.727
convulsion*	9	0.345
tremor*	9	0.345
cerebral vascular event*	6	0.230
PSYCHIATRIC DISORDERS		
anxiety*	101	3.867
abnormal dreams*	19	0.727
libido decreased	19	0.727
RENAL AND URINARY DISORDERS		
renal failure*	31	1.187
haematuria*	20	0.766
nephritis*	3	0.115
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
erectile dysfunction*	34	1.668[1]
menstrual disorders - amenorrhea, menorrhagia*	10	1.742[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
rash including maculopapular rash*	99	3.790
dermatitis/rash including eczema and seborrheic dermatitis*	50	1.914
night sweats*	42	1.608
pruritus*	29	1.110
alopecia	10	0.383
capillaritis and vasculitis*	3	0.115
VASCULAR DISORDERS		
hypertension*	47	1.799
deep vein thrombosis*	17	0.651

*Represents a medical concept including several similar MedDRA PTs

[1.] Percentage of male population (N=2,038)

[2.] Percentage of female population (N=574)

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy including Kaletra with Grade 3 to 4 laboratory abnormalities are presented in Tables 7 and 8.

Table 7: 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 twice daily + d4T +3TC (N = 326)**	**Nelfinavir 750 mg three times daily + d4T + 3TC (N = 327)**	**Kaletra 800/200 mg once daily + TDF + FTC (N = 115)**	**Kaletra 400/100 mg twice daily + TDF + FTC (N = 75)**	**Kaletra twice daily + d4T + 3TC (N = 100)**	**Kaletra once daily + TDF +FTC (N=333)**	**Kaletra twice daily + TDF +FTC (N=331)**
Chemistry	**High**							
Glucose	> 250 mg/dL	2%	2%	3%	1%	4%	0%	<1%
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)

d4T = Stavudine; 3TC = Lamivudine; TDF = Tenofovir; FTC = Emtricitabine

Table 8: 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 twice daily + NVP + NRTIs (N=148)**	**Investigator-selected protease inhibitor(s) + NVP + NRTIs (N=140)**	**Kaletra twice daily + NNRTI + NRTIs (N=127)**	**Kaletra 800/200 mg once daily + NRTIs (N=300)**	**Kaletra 400/100 mg twice daily +NRTIs (N=299)**
Chemistry	**High**					
Glucose	> 250 mg/dL	1%	2%	5%	2%	2%
Total Bilirubin	> 3.48 mg/dL	1%	3%	1%	1%	1%
SGOT/AST[4]	> 180 U/L	5%	11%	8%	3%	2%
SGPT/ALT[4]	> 215 U/L	6%	13%	10%	2%	2%
GGT	> 300 U/L	N/A	N/A	29%	N/A	N/A
Total Cholesterol	> 300 mg/dL	20%	21%	39%	6%	7%
Triglycerides	> 750 mg/dL	25%	21%	36%	5%	6%
Amylase	> 2 x ULN	4%	8%	8%	4%	4%
Lipase	> 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 twice daily (n=29) or 533/133 mg twice daily (n=28) for 84 weeks. Patients received Kaletra in combination with NRTIs and efavirenz.

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

[4] Criterion for Study 802 was >5x ULN (AST/ALT)

NVP = nevirapine

Paediatric Population

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 eight 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 aged 6 months to 12 years or treated with combination therapy including Kaletra in Study M98-940 with Grade 3 to 4 laboratory abnormalities are presented in Table 9.

Table 9: Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% Paediatric Patients

Variable	**Limit[+]**	**Kaletra Twice Daily + 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%

Table 9: Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% Paediatric Patients		
Variable	**Limit[+]**	**Kaletra Twice Daily + RTIs (n=100)**
Haematology	**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.		

Post-Marketing 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 of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Overdoses with Kaletra oral solution have been reported. The following events have been reported in association with unintended overdoses in preterm neonates: complete AV block, cardiomyopathy, lactic acidosis, and acute renal failure. Healthcare professionals should be aware that Kaletra oral solution is highly concentrated and contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v), and therefore, should pay special attention to accurate calculation of the dose of Kaletra, transcription of the medication order, dispensing information and dosing instructions to minimise the risk for medication errors and overdose. This is especially important for infants and young children (see sections 6.1 List of excipients, 4.2 Dose and method of administration, and 4.4 Special warnings and precautions for use).

Human experience of acute overdosage with Kaletra is limited. Treatment of overdose with Kaletra should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Kaletra. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since Kaletra is highly protein bound, dialysis is unlikely

to be beneficial in significant removal of the drug. However, dialysis can remove both alcohol and propylene glycol in cases of overdosage with Kaletra oral solution.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antivirals for systemic use, antivirals for treatment of HIV infections, combinations, ATC code: J05AR10.

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.

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 μ/mL, 1 μ/mL equals 1.6 microM) and ranged from 4 to 11 nM (0.003 to 0.007 μ/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 μ/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 naïve patients has not yet been characterised. In a Phase III study of 653 antiretroviral treatment naïve 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 naïve 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 naïve 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

Virologic response to Kaletra has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. Table 10 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 10: 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 11 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 10 present at baseline (see section 5.1-Clinical Studies). There are insufficient data to support once daily administration of Kaletra for adult patients with three or more lopinavir-associated mutations.

Table 11: 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 Studies

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-naïve 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.

Clinical Efficacy and Safety Results

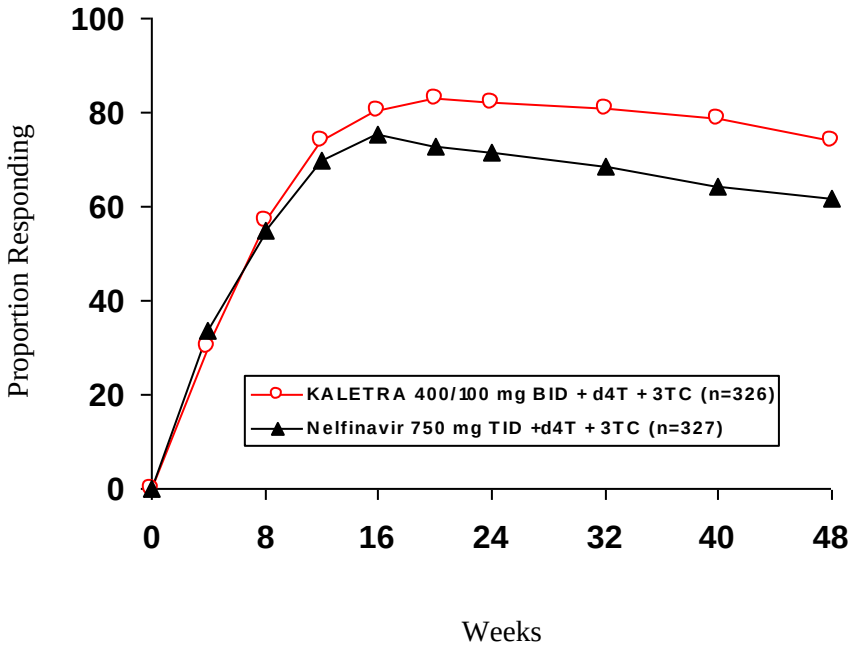
Patients without Prior Antiretroviral Therapy

Study M98-863: Kaletra capsules twice daily + stavudine + lamivudine compared to nelfinavir three times daily + stavudine + lamivudine.

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

Treatment response and outcomes of randomised treatment are presented in Figure 1 and Table 12, 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 12: 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 13.

Table 13: 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

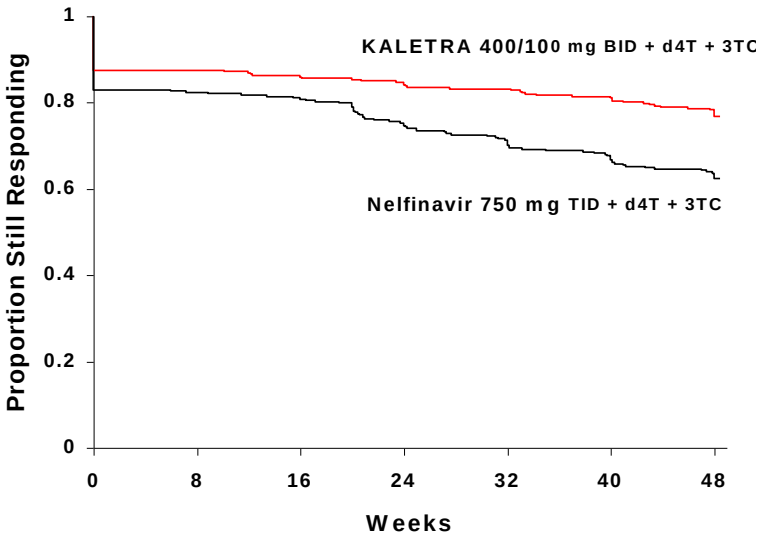
[1] Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

[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 twice daily + 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 twice daily + stavudine + lamivudine

Study M97-720 was a randomised, blinded, multicentre trial evaluating treatment with Kaletra capsules at three dose levels (Group I: 200/100 mg twice daily and 400/100 mg twice daily; Group II: 400/100 mg twice daily and 400/200 mg twice daily) plus lamivudine (150 mg twice daily) and stavudine (40 mg twice daily) in 100 patients. All patients were converted to open label Kaletra at the 400/100 mg twice daily dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 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.

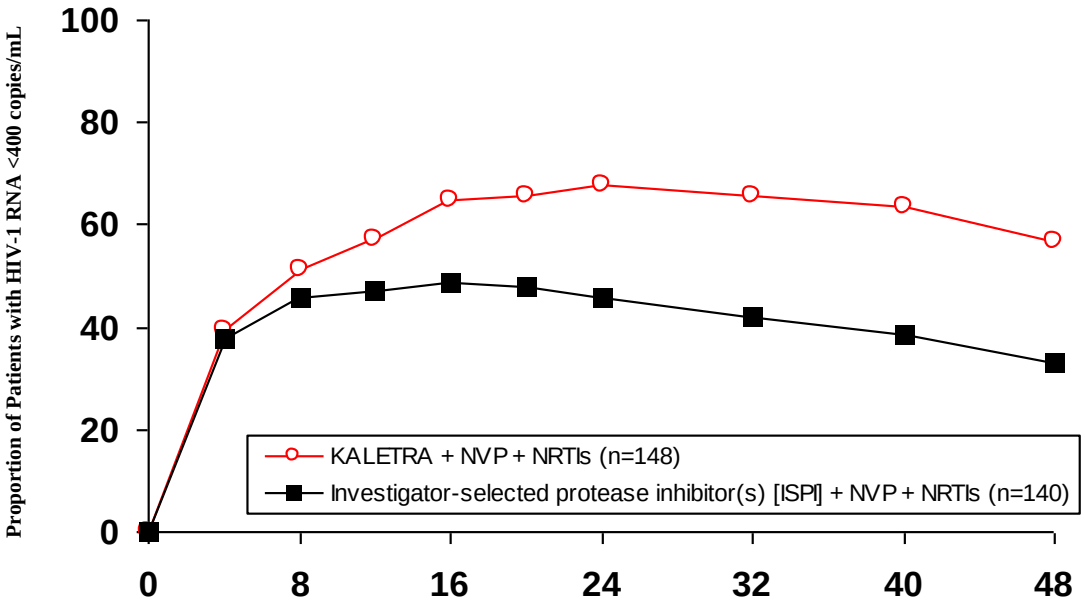
Patients with Prior Antiretroviral Therapy

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

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

Treatment response and outcomes of randomised treatment through Week 48 are presented in Figure 3 and Table 14, 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 14: 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 3.

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 twice daily + nevirapine + NRTIs

Study M97-765 was a randomised, blinded, multicentre trial evaluating treatment with Kaletra capsules at two dose levels (400/100 mg twice daily and 400/200 mg twice daily) plus nevirapine (200 mg twice daily) and two NRTIs in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI) naïve 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. Twenty-seven (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 twice daily + NRTIs in Antiretroviral-Experienced, HIV-1 infected patients

Study M06-802 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 15.

Table 15: 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%
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 Population

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 naïve (44%) and experienced (56%) paediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. 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. Naïve patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of 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 naïve patients and 71% for antiretroviral-experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm^3 for antiretroviral naïve and 284 cells/mm^3 for antiretroviral-experienced patients treated through 48 weeks. Premature discontinuations were noted in two (2%) subjects prior to week 48. One of these was considered by the investigator to be "unrelated" to study treatment, the second "possibly" related to study treatment.

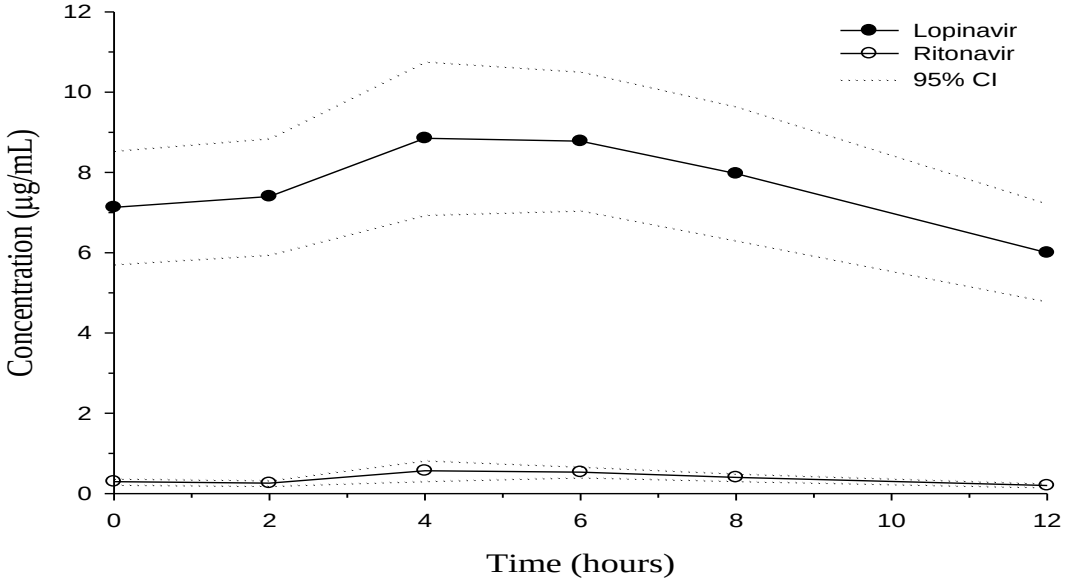
Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving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

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 twice daily yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg twice daily. The *in-vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Kaletra is due to lopinavir.

Figure 4 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after Kaletra 400/100 mg twice daily 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

In a pharmacokinetic study in HIV-positive subjects (n=18), multiple dosing with 400/100 mg Kaletra tablets twice daily with or without food for 2 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 12.3 ± 5.4 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 µg/mL and minimum concentration within a dosing interval was 5.6 ± 4.5 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 113.2 ± 60.5 µg·h/mL. 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, therefore, Kaletra tablets may be taken with or without food.

Administration of Kaletra oral solution under non-fasting conditions, with a moderate fat meal (500 to 682 kcal, 23 to 25% 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, 56% 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 twice daily, and is similar between healthy volunteers and HIV-positive patients.

Biotransformation

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 active substance. 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.

Elimination

Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and 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).

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 μg/mL, occurring approximately 6 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 5.4 μg/mL and minimum concentration within a dosing interval was 3.2 ± 3.4 μg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 206.5 ± 89.7 μg·h/mL.

Effects on Electrocardiogram

QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled cross-over 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) millisecond (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 section 4.4 Special warnings and precautions for use).

Special Populations

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 twice daily and 230/57.5 mg/m^2 twice daily 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 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine).

The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 μg•h/mL, 8.2 ± 2.9 μg•h/mL and 3.4 ± 2.1 μg•h/mL, respectively after Kaletra 230/57.5 mg/m^2 twice daily without nevirapine (N=12), and were 85.8 ± 36.9 μg•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5 μg•h/mL, respectively after 300/75 mg/m^2 twice daily with nevirapine (N=12). The nevirapine regimen was 7 mg/kg twice daily (six months to eight years) or 4 mg/kg twice daily (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 section 4.4 - Hepatic Impairment).

Medicine Interactions

(Also see sections 4.3 Contraindications and 4.5 Interactions with other medicines and other forms of interaction).
Kaletra is an inhibitor of the P450 isoform CYP3A *in-vitro*. Co-administration of Kaletra and other medicines primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicines, which could increase or prolong its therapeutic and adverse effects.

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

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

Kaletra is metabolised by CYP3A. Medicines that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, co-administration of Kaletra and other medicines that inhibit CYP3A may increase lopinavir plasma concentrations.

Interaction studies were performed with Kaletra and other medicines likely to be co-administered and some medicines 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 16 (effect of other medicines on lopinavir) and Table 17 (effect of Kaletra on other medicines). The effects of other medicines on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see section 4.5 Interactions with other medicines and other forms of interaction.

Table 16: Medicine Interactions

Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Medicine (see section 4.5 for Recommended Alterations in Dose or Regimen)

Co-administered Medicine	Dose of co-administered Medicine (mg)	Dose of Kaletra (mg)	N	Ratio (with/without co-administered medicine) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	750 twice daily; 10 days	400/100 capsule twice daily; 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 twice daily; 14 days	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Boceprevir	800 eight-hourly; 6 days	400/100 tablet twice daily; 22 days	39	0.70 (0.65, 0.77)	0.66 (0.60, 0.72)	0.57 (0.49, 0.65)
Efavirenz[1]	600 nocte; 9 days	400/100 capsule twice daily; 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 twice daily; 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 twice daily; 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 twice daily; 16 days	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 twice daily; 10 days	400/100 capsule twice daily; 21 days	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 twice daily; steady-state (> 1 year)[2]	400/100 capsule twice daily; steady-state (> 1 year)	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)

Table 16: Medicine Interactions

Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Medicine (see section 4.5 for Recommended Alterations in Dose or Regimen)

Co-administered Medicine	Dose of co-administered Medicine (mg)	Dose of Kaletra (mg)	N	Ratio (with/without co-administered medicine) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
	7 mg/kg or 4 mg/kg once daily, 2 weeks; twice daily 1 week[3]	300/75 mg/m^2 oral solution twice daily; 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 twice daily; 10 days	12	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 twice daily; 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 twice daily; 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	0.98 (0.95, 1.01)	0.96 (0.90, 1.02)	0.85 (0.67, 1.08)
Rifabutin	150 daily; 10 days	400/100 capsule twice daily; 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 twice daily; 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 twice daily; 9 days[4]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)

Table 16: Medicine Interactions

Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Medicine (see section 4.5 for Recommended Alterations in Dose or Regimen)

Co-administered Medicine	Dose of co-administered Medicine (mg)	Dose of Kaletra (mg)	N	Ratio (with/without co-administered medicine) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
	600 daily; 14 days	400/400 capsule twice daily; 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 section 4.4 Special warnings and precautions for use)					
Ritonavir[2]	100 twice daily; 3 to 4 weeks	400/100 capsule twice daily; 3 to 4 weeks	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Telaprevir	750 eight-hourly; 10 days	400/100 twice daily; 20 days	12	0.96 (0.87, 1.05)	1.06 (0.96, 1.17)	1.14 (0.96, 1.36)

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 twice daily as 533/133 twice daily x 1 day, 667/167 twice daily x 1 day, then 800/200 twice daily x 7 days, compared to 400/100 twice daily x 10 days alone.

5 Titrated to 400/400 twice daily as 400/200 twice daily x 1 day, 400/300 twice daily x 1 day, then 400/400 twice daily x 7 days, compared to 400/100 twice daily x 10 days alone.

* Parallel group design; n for Kaletra + co-administered medicine, n for Kaletra alone.

Table 17: Medicine Interactions

Pharmacokinetic Parameters for Co-administered Medicine in the Presence of Kaletra (see section 4.5 for Recommended Alterations in Dose or Regimen)

Co-administered Medicine	Dose of Co-administered Medicine (mg)	Dose of Kaletra (mg)	N	Ratio (with/without Kaletra) of Co-administered Medicine Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir[1]	750 twice daily; 10 days combo vs. 1200 twice daily; 14 days alone	400/100 capsule twice daily; 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 twice daily; 14 days	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Boceprevir	800 eight-hourly; 6 days	400/100 tablet twice daily; 22 days	39	0.50 (0.45, 0.55)	0.55 (0.49, 0.61)	0.43 (0.36, 0.53)
Desipramine[2]	100 single dose	400/100 capsule twice daily; 10 days	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	NA
Efavirenz	600 nocte; 9 days	400/100 capsule twice daily; 9 days	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyloestradiol	35 micrograms daily; 21 days (Brevinor-1®)	400/100 capsule twice daily; 14 days	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir[1]	600 twice daily, 10 days combo non-fasting vs. 800 three times daily, 5 days alone fasting	400/100 capsule twice daily; 15 days	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)

Table 17: Medicine Interactions

Pharmacokinetic Parameters for Co-administered Medicine in the Presence of Kaletra

(see section 4.5 for Recommended Alterations in Dose or Regimen)

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**Dose of Kaletra (mg)**	**N**	**Ratio (with/without Kaletra) of Co-administered Medicine Pharmacokinetic Parameters (90% CI); No Effect = 1.00**		
				C_{max}	AUC	C_{min}
Ketoconazole	200 single dose	400/100 capsule twice daily; 16 days	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	NA
Lamotrigine	100 twice daily, 12 days vs. 100 twice daily, 8 days alone	400/100 capsule twice daily; 12 days	18	0.54 (0.49, 0.58)	0.5 (0.47, 0.54)	0.44 (0.40, 0.47)
	200 twice daily, 9 days vs. 100 twice daily, 8 days alone	400/100 capsule twice daily; 9 days	15	1.03 (0.90, 1.17)	0.91 (0.82, 1.02)	0.79 (0.69, 0.90)
Maraviroc	300 twice daily	400/100 capsule twice daily	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)
Methadone	5 single dose	400/100 capsule twice daily; 10 days	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	NA
Nelfinavir[1] M8 metabolite	1000 twice daily, 10 days combo vs. 1250 twice daily, 14 days alone	400/100 capsule twice daily; 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; twice daily, 6 days	400/100 capsule twice daily; 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 twice daily; 14 days	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)

Table 17: Medicine Interactions

Pharmacokinetic Parameters for Co-administered Medicine in the Presence of Kaletra

(see section 4.5 for Recommended Alterations in Dose or Regimen)

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**Dose of Kaletra (mg)**	**N**	**Ratio (with/without Kaletra) of Co-administered Medicine Pharmacokinetic Parameters (90% CI); No Effect = 1.00**		
				C_{max}	AUC	C_{min}
Pravastatin	20 daily; 4 days	400/100 capsule twice daily; 14 days	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	NA
Rifabutin	150 daily 10 days combo vs. 300 daily, 10 days; alone	400/100 capsule twice daily; 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 twice daily, 10 days combo vs. 1200 three times daily, 5 days alone,	400/100 capsule twice daily; 15 days	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
		400/100 capsule twice daily; 20 days				
	1200 twice daily, 5 days combo vs. 1200 three times daily, 5 days alone		10	6.44 (5.59, 7.41)	9.91 (8.28, 11.86)	16.54 (10.91, 25.08)
Telaprevir	750 eight-hourly, ; 10 days	400/100 twice daily; 20 days	12	0.47 (0.41, 0.52)	0.46 (0.41, 0.52)	0.48 (0.40, 0.56)

Table 17: Medicine Interactions
Pharmacokinetic Parameters for Co-administered Medicine in the Presence of Kaletra
(see section 4.5 for Recommended Alterations in Dose or Regimen)

Co-administered Medicine	Dose of Co-administered Medicine (mg)	Dose of Kaletra (mg)	N	Ratio (with/without Kaletra) of Co-administered Medicine Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

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

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

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

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

NA = not available.

5.3 Preclinical Safety Data

Acute, Subacute and Chronic Toxicity

Repeat-dose toxicity studies in rodents and dogs identified major target organs as the liver, kidney, thyroid, spleen and circulating red blood cells. Hepatic changes indicated cellular swelling with focal degeneration. While exposure eliciting these changes were comparable to human clinical exposure, dosages in animals were over 6-fold the recommended clinical dose. Mild renal tubular degeneration was confined to mice exposed with at least twice the recommended human exposure; the kidney was unaffected in rats and dogs. Reduced serum thyroxine led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs. Enlarged spleens with histiocytosis were seen in rats but not in other species. Serum cholesterol was elevated in rodents but not in dogs, while triglycerides were elevated only in mice.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies of lopinavir/ritonavir in mice revealed a non-genotoxic, mitogenic induction of liver tumours, generally considered to have little relevance to human risk. Carcinogenicity studies in rats revealed no tumorigenic findings. Lopinavir was not found to be mutagenic or clastogenic in a battery of *in-vitro* assays including the Ames bacterial reverse mutation assay, the mouse lymphoma assay, and chromosomal aberration assays in human lymphocytes. Lopinavir/ritonavir was not found to be mutagenic or clastogenic in *in-vivo* assays using the mouse micronucleus assay.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Kaletra 100/25 mg Film-Coated Tablets

Tablet core

Copovidone
Silica-colloidal anhydrous
Sorbitan monolaurate
Sodium stearylfumarate

Film-coating (Opadry Yellow 85F32450)

Polyvinyl alcohol
Titanium dioxide
Talc
Macrogols 3350
Iron oxide yellow CI 77492 (E172)

Kaletra 200/50 mg Film-Coated Tablets

Tablet core

Copovidone
Silica-colloidal anhydrous
Sorbitan monolaurate
Sodium stearylfumarate

Film-coating (Opadry Yellow 16B22295)

Hypromellose
Titanium dioxide
Macrogol 400
Hydroxypropylcellulose
Talc
Silica-colloidal anhydrous
Macrogol 3350
Iron oxide yellow CI 77492 (E172)
Polysorbate 80

Kaletra Oral Solution

Acesulfame potassium
Castor oil – PEG 40 hydrogenated

Citric acid
Cotton Candy, Artificial 30-92-0011 (contains ethyl maltol, ethyl vanillin, acetoin, dihydrocoumarin and propylene glycol)
Ethanol absolute
Glycerol
High fructose maize syrup
Menthol
Magnasweet-110 flavour (contains monoammonium glycyrrhizinate and glycerol)
Peppermint oil
Povidone
Propylene glycol
Purified water
Saccharin sodium
Sodium chloride
Sodium citrate dihydrate
Vanilla, Natural and Artificial 33869 (contains p-hydroxybenzoic acid, p-hydroxybenzaldehyde, vanillic acid, vanillin, heliotrope and ethyl vanillin).

6.2 Incompatibilities

Film-Coated Tablets

Not applicable.

Oral Solution

Products containing alcohol, like Kaletra oral solution, are not recommended for use with polyurethane feeding tubes due to potential incompatibility.

6.3 Shelf-Life

Film-Coated Tablets

Bottle - 3 years
Blister pack - 2 years

Oral Solution

2 years

6.4 Special Precautions for Storage

Film-Coated Tablets

Bottle - Store at or below 30°C
Blister pack - Store at or below 25°C

Oral Solution

Store at 2°C to 8°C (Refrigerate, do not freeze) until dispensed.
Refrigeration of Kaletra oral solution by the patient is not required if used within 42 days and stored at or below 25°C; however, refrigeration by the patient is recommended whenever possible.
Avoid exposure to excessive heat and freezing.

6.5 Nature and Contents of Container

Film-Coated Tablets

Kaletra 100/25 mg film-coated tablets are supplied in High Density Polyethylene (HDPE) bottles closed with polypropylene caps containing 60 tablets.
Kaletra 200/50 mg film-coated tablets are supplied in High Density Polyethylene (HDPE) bottles closed with polypropylene caps containing 120 tablets. Also in blister packs (PVC/Aclar) with aluminium foil lidding containing 120 tablets*.

Oral Solution

Kaletra 80/20 mg per mL oral solution is available in an amber coloured polyethylene terephthalate (PET) 60 mL bottle with polypropylene child-resistant cap. Each pack contains five bottles of 60 mL oral solution.

*Not all presentations are available.

6.6 Special Precautions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand
Phone: 0800 900 030

9. DATE OF FIRST APPROVAL

Kaletra 100/25 mg film-coated tablets - 2 October 2008
Kaletra 200/50 mg film-coated tablets - 5 October 2006
Kaletra 80/20 mg per mL oral solution - 31 July 2003

10. DATE OF REVISION OF THE TEXT

6 May 2020

Version 30

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Minor spelling and formatting changes throughout.
4.3 Contraindications	Clarification from the latest Company Core Data Sheet (CCDS) provided
4.4 Special warnings and precautions for use	Additional information provided and text updated throughout these sections, in line with the latest CCDS.
4.5 Interactions with other medicines and other forms of interactions	
4.6 Fertility, pregnancy and lactation	
4.8 Undesirable effects	
4.9 Overdose	
5 Pharmacological properties	
4.8 Undesirable effects	Nephrolithiasis added under Post-Marketing Experience, in line with the latest CCDS.