1. NAME OF THE MEDICINAL PRODUCT

RITOCOM (Lopinavir and Ritonavir Tablets USP 100 mg /25 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains Ritonavir USP 50 mg, Lopinavir USP 200 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Description: Yellow, capsule shaped, biconvex film coated tablets, debossed with 'H' on one side and 'L7' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lopinavir and Ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children above the age of 2 years.

The choice of Lopinavir and Ritonavir to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Lopinavir and Ritonavir should be prescribed by physicians who are experienced in the treatment of HIV infection.

Lopinavir and Ritonavir tablets must be swallowed whole and not chewed, broken or crushed.

Posology

Adults and adolescents

The standard recommended dosage of Lopinavir and Ritonavir tablets is 400/100 mg (two 200/50 mg) tablets twice daily taken with or without food. In adult patients, in cases where once-daily dosing is considered necessary for the management of the patient, Lopinavir and Ritonavir

tablets may be administered as 800/200 mg (four 200/50 mg tablets) once daily with or without food. The use of a once-daily dosing should be limited to those adult patients having only very few protease inhibitor (PI) associated mutations (i.e. less than 3 PI mutations in line with clinical trial results, see section 5.1 for the full description of the population) and should take into account the risk of a lesser sustainability of the virologic suppression (see section 5.1) and higher risk of diarrhea (see section 4.8) compared to the recommended standard twice-daily dosing. An oral solution is available to patients who have difficulty swallowing. Refer to the Summary of Product Characteristics for Kaletra oral solution for dosing instructions.

Paediatric population (2 years of age and above)

The adult dose of Kaletra tablets (400/100 mg twice daily) may be used in children 40 kg or greater or with a Body Surface Area (BSA)* greater than 1.4 m2. For children weighing less than 40 kg or with a BSA between 0.5 and 1.4 m2 and able to swallow tablets, please refer to the Lopinavir and Ritonavir 100 mg/25 mg tablets Summary of Product Characteristics. For children unable to swallow tablets, please refer to the Lopinavir and Ritonavir oral solution Summary of Product Characteristics. Based on the current data available, Lopinavir and Ritonavir should not be administered once daily in paediatric patients (see section 5.1).

* Body surface area can be calculated with the following equation:

BSA (m2) = √ (Height (cm) X Weight (kg) / 3600)

Children less than 2 years of age

The safety and efficacy of Lopinavir and Ritonavir in children aged less than 2 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Concomitant Therapy: Efavirenz or nevirapine

The following table contains dosing guidelines for Lopinavir and Ritonavir tablets based on BSA when used in combination with efavirenz or nevirapine in children.

Paediatric dosing guidelines with concomitant efavirenz or nevirapine	
Body Surface Area (m2)	Recommended lopinavir/ritonavir dosing (mg) twice daily. The adequate dosing may be achieved with the two available strengths of Kaletra tablets: 100/25 mg and 200/50 mg.*
≥ 0.5 to < 0.8	200/50 mg

≥ 0.8 to < 1.2	300/75 mg
≥ 1.2 to < 1.4	400/100 mg
≥ 1.4	500/125 mg

* Lopinavir and Ritonavir tablets must not be chewed, broken or crushed.

Hepatic impairment

In HIV-infected patients with mild to moderate hepatic impairment, an increase of approximately 30% in lopinavir exposure has been observed but is not expected to be of clinical relevance (see section 5.2). No data are available in patients with severe hepatic impairment. Lopinavir and Ritonavir must not be given to these patients (see section 4.3).

Renal impairment

Since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because lopinavir and ritonavir are highly protein bound, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

Pregnancy and postpartum

• No dose adjustment is required for lopinavir/ritonavir during pregnancy and postpartum.

• Once-daily administration of lopinavir/ritonavir is not recommended for pregnant women due to the lack of pharmacokinetic and clinical data.

Method of administration

Lopinavir and Ritonavir tablets are administered orally and must be swallowed whole and not chewed, broken or crushed. Kaletra tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Severe hepatic insufficiency.

Lopinavir and Ritonavir contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Kaletra should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. These medicinal products include:

Medicinal product class	**Medicinal products within class**	**Rationale**

Concomitant medicinal product levels increased		
Alpha1-adrenoreceptor antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension. The concomitant administration with alfuzosin is contraindicated (see section 4.5).
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
Antiarrhythmics	Amiodarone, dronedarone	Increased plasma concentrations of amiodarone and dronedarone. Thereby, increasing the risk of arrhythmias or other serious adverse reactions.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid. The concomitant administration with fusidic acid is contraindicated in dermatological infections. (see section 4.5).
Anti-gout	Colchicine	Increased plasma concentrations of colchicine. Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see sections 4.4 and 4.5).
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antipsychotics/ Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
	Pimozide	Increased plasma concentrations of pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from this agent.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 4.5).
Ergot alkaloids	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
GI motility agent	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent.
HMG Co-A Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of

		myopathy including rhabdomyolysis (see section 4.5).
Phosphodiesterase (PDE5) inhibitors	Avanafil	Increased plasma concentrations of avanafil (see sections 4.4 and 4.5)
	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil-associated adverse events (which include hypotension and syncope). See section 4.4 and section 4.5 for co-administration of sildenafil in patients with erectile dysfunction.
	Vardenafil	Increased plasma concentrations of vardenafil (see sections 4.4 and 4.5)
Sedatives/hypnotics	Oral midazolam, triazolam	Increased plasma concentrations of oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. For caution on parenterally administered midazolam, see section 4.5.
Lopinavir/ritonavir medicinal product level decreased		
Herbal products	St. John's wort	Herbal preparations containing St John's wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of lopinavir and ritonavir (see section 4.5).

4.4 Special warnings and precautions for use

Patients with coexisting conditions

Hepatic impairment:

The safety and efficacy of Lopinavir and Ritonavir has not been established in patients with significant underlying liver disorders. Lopinavir and Ritonavir is contraindicated in patients with severe liver impairment (see section 4.3). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should

be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and in individuals treated for post-exposure prophylaxis as early as 7 days after the initiation of lopinavir/ritonavir in conjunction with other antiretroviral agents. In some cases the hepatic dysfunction was serious.

Appropriate laboratory testing should be conducted prior to initiating therapy with lopinavir/ritonavir and close monitoring should be performed during treatment.

Renal impairment

Since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because lopinavir and ritonavir are highly protein bound, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

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 if treatment had been discontinued. A causal relationship had been evoked, although the mechanism of action had not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Pancreatitis

Cases of pancreatitis have been reported in patients receiving Lopinavir and Ritonavir, including those who developed hypertriglyceridaemia. In most of these cases patients have had a prior history of pancreatitis and/or concurrent therapy with other medicinal products associated with pancreatitis. Marked triglyceride elevation is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and Lopinavir and Ritonavir therapy should be suspended if a diagnosis of pancreatitis is made

(see section 4.8).

Immune Reconstitution Inflammatory Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymtomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jiroveci pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

PR interval prolongation

Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atroventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. Lopinavir and Ritonavir should be used with caution in such patients (see section 5.1).

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is

made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Interactions with medicinal products

Kaletra contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Lopinavir and Ritonavir is likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. These increases of plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events (see sections 4.3 and 4.5).

Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with lopinavir/ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with lopinavir/ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.5 and refer to the bedaquiline SmPC).

Co-administration of delamanid with a strong inhibitor of CYP3A (as lopinavir/ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.5 and refer to the delamanid SmPC).

Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir. Concomitant administration with colchicine is contraindicated in patients with renal and/or hepatic impairment (see sections 4.3 and 4.5).

The combination of Lopinavir and Ritonavir with:

- tadalafil, indicated for the treatment of pulmonary arterial hypertension, is not recommended (see section 4.5);
- riociguat is not recommended (see section 4.5);
- vorapaxar is not recommended (see section 4.5);
- fusidic acid in osteo-articular infections is not recommended (see section 4.5);
- salmeterol is not recommended (see section 4.5);
- rivaroxaban is not recommended (see section 4.5).

The combination of Lopinavir and Ritonavir with atorvastatin is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring. Caution must also be exercised and reduced doses should be considered if Lopinavir and Ritonavir is used concurrently with rosuvastatin. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

PDE5 inhibitors

Particular caution should be used when prescribing sildenafil or tadalafil for the treatment of erectile dysfunction in patients receiving Lopinavir and Ritonavir Co-administration of Lopinavir and Ritonavir with these medicinal products is expected to substantially increase their concentrations and may result in associated adverse events such as hypotension, syncope, visual changes and prolonged erection (see section 4.5). Concomitant use of avanafil or vardenafil and lopinavir/ritonavir is contraindicated (see section 4.3). Concomitant use of sildenafil prescribed for the treatment of pulmonary arterial hypertension with Lopinavir and Ritonavir is contraindicated (see section 4.3).

Particular caution must be used when prescribing Lopinavir and Ritonavir and medicinal products known to induce QT interval prolongation such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. Indeed, Lopinavir and Ritonavir could increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac adverse reactions. Cardiac events have been reported with Kaletra in preclinical studies; therefore, the potential cardiac effects of Lopinavir and Ritonavir cannot be currently ruled out (see sections 4.8 and 5.3).

Co-administration of Lopinavir and Ritonavir with rifampicin is not recommended. Rifampicin in combination with Lopinavir and Ritonavir causes large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect. Adequate exposure to lopinavir/ritonavir may be achieved when a higher dose of Lopinavir and Ritonavir is used but this is associated with a higher risk of liver and gastrointestinal toxicity. Therefore, this co-administration should be avoided unless judged strictly necessary (see section 4.5)

Concomitant use of Lopinavir and Ritonavir and fluticasone or other glucocorticoids that are

metabolised by CYP3A4, such as budesonide and triamcinolone, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Other

Lopinavir and Ritonavir is not a cure for HIV infection or AIDS. While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines. People taking Lopinavir and Ritonavir may still develop infections or other illnesses associated with HIV disease and AIDS.

4.5 Interaction with other medicinal products and other forms of interaction

Kaletra contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A in vitro. Co-administration of Lopinavir and Ritonavir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse reactions. Lopinavir and Ritonavir does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations (see section 4.3).

Lopinavir and Ritonavir has been shown in vivo to induce its own metabolism and to increase the biotransformation of some medicinal products metabolised by cytochrome P450 enzymes (including CYP2C9 and CYP2C19) and by glucuronidation. This may result in lowered plasma concentrations and potential decrease of efficacy of co-administered medicinal products.

Medicinal products that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in section 4.3.

All interaction studies, when otherwise not stated, were performed using Lopinavir and Ritonavir capsules, which gives an approximately 20% lower exposure of lopinavir than the 200/50 mg tablets.

Known and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the table below.

Interaction table

Interactions between Lopinavir and Ritonavir and co-administered medicinal products are listed

in the table below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”,once daily as “QD”, twice daily as “BID” and three times daily as "TID").

Unless otherwise stated, studies detailed below have been performed with the recommended dosage of lopinavir/ritonavir (i.e. 400/100 mg twice daily).

Co-administered drug by therapeutic area	Effects on drug levels Geometric Mean Change (%) in AUC, Cmax, Cmin Mechanism of interaction	Clinical recommendation concerning co-administration with Kaletra
Antiretroviral Agents		
Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs)		
Stavudine, Lamivudine	Lopinavir: ↔	No dose adjustment necessary.
Abacavir, Zidovudine	Abacavir, Zidovudine: Concentrations may be reduced due to increased glucuronidation by Kaletra.	The clinical significance of reduced abacavir and zidovudine concentrations is unknown.
Tenofovir, 300 mg QD	Tenofovir: AUC: ↑ 32% Cmax: ↔ Cmin: ↑ 51% Lopinavir: ↔	No dose adjustment necessary. Higher tenofovir concentrations could potentiate tenofovir associated adverse events, including renal disorders.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz, 600 mg QD	Lopinavir: AUC: ↓ 20% Cmax: ↓ 13% Cmin: ↓ 42%	The Kaletra tablets dosage should be increased to 500/125 mg twice daily when co-administered with efavirenz. Kaletra must not be administered once daily in combination with efavirenz.
Efavirenz, 600 mg QD (Lopinavir/ritonavir 500/125 mg BID)	Lopinavir: ↔ (Relative to 400/100 mg BID administered alone)	
Nevirapine, 200 mg BID	Lopinavir: AUC: ↓ 27% Cmax: ↓ 19% Cmin: ↓ 51%	The Kaletra tablets dosage should be increased to 500/125 mg twice daily when co-administered with nevirapine. Kaletra must not be administered once daily in combination with nevirapine.
Etravirine (Lopinavir/ritonavir tablet 400/100 mg BID)	Etravirine : AUC: ↓ 35% Cmin: ↓ 45% Cmax: ↓ 30% Lopinavir :	No dose adjustment necessary

	AUC: ↔ Cmin: ↓ 20% Cmax: ↔	
Rilpivirine (Lopinavir/ritonavir capsule 400/100 mg BID)	Rilpivirine: AUC: ↑ 52% Cmin: ↑ 74% Cmax: ↑ 29% Lopinavir: AUC: ↔ Cmin: ↓ 11% Cmax: ↔ (inhibition of CYP3A enzymes)	Concomitant use of Kaletra with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required.
HIV CCR5 – antagonist		
Maraviroc	Maraviroc: AUC: ↑ 295% Cmax: ↑ 97% Due to CYP3A inhibition by lopinavir/ritonavir.	The dose of maraviroc should be decreased to 150 mg twice daily during co-administration with Kaletra 400/100 mg twice daily.
Integrase inhibitor		
Raltegravir	Raltegravir: AUC: ↔ Cmax: ↔ C12: ↓ 30% Lopinavir: ↔	No dose adjustment necessary
Co-administration with other HIV protease inhibitors (PIs) According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.		
Fosamprenavir/ ritonavir (700/100 mg BID) (Lopinavir/ritonavir 400/100 mg BID) or Fosamprenavir (1400 mg BID) (Lopinavir/ritonavir 533/133 mg BID)	Fosamprenavir: Amprenavir concentrations are significantly reduced.	Co-administration of increased doses of fosamprenavir (1400 mg BID) with lopinavir/ritonavir (533/133 mg BID) to protease inhibitor-experienced patients resulted in a higher incidence of gastrointestinal adverse events and elevations in triglycerides with the combination regimen without increases in virological efficacy, when compared with standard doses of fosamprenavir/ritonavir. Concomitant administration of these medicinal products is not recommended. Kaletra must not be administered once daily in combination with amprenavir.
Indinavir, 600 mg	Indinavir:	The appropriate doses for this combination,

BID	AUC: ↔ Cmin: ↑ 3.5-fold Cmax: ↓ (relative to indinavir 800 mg TID alone) Lopinavir: ↔ (relative to historical comparison)	with respect to efficacy and safety, have not been established.
Saquinavir 1000 mg BID	Saquinavir: ↔	No dose adjustment necessary.
Tipranavir/ritonavir (500/100 mg BID)	Lopinavir: AUC: ↓ 55% Cmin: ↓ 70% Cmax: ↓ 47%	Concomitant administration of these medicinal products is not recommended.
Acid reducing agents		
Omeprazole (40 mg QD)	Omeprazole: ↔ Lopinavir: ↔	No dose adjustment necessary
Ranitidine (150 mg single dose)	Ranitidine: ↔	No dose adjustment necessary
Alpha1 adrenoreceptor antagonist		
Alfuzosin	Alfuzosin: Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of alfuzosin are expected to increase.	Concomitant administration of Kaletra and alfuzosin is contra-indicated (see section 4.3) as alfuzosin-related toxicity, including hypotension, may be increased.
Analgesics		
Fentanyl	Fentanyl: Increased risk of side-effects (respiratory depression, sedation) due to higher plasma concentrations because of CYP3A4 inhibition by Kaletra	Careful monitoring of adverse effects (notably respiratory depression but also sedation) is recommended when fentanyl is concomitantly administered with Kaletra.
Antianginal		
Ranolazine	Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of ranolazine are expected to increase.	The concomitant administration of Kaletra and ranolazine is contraindicated (see section 4.3).
Antiarrhythmics		
Amiodarone, Dronedarone	Amiodarone, Dronedarone: Concentrations may be	Concomitant administration of Kaletra and amiodarone or dronedarone is

	increased due to CYP3A4 inhibition by Kaletra.	contraindicated (see section 4.3) as the risk of arrhythmias or other serious adverse reactions may be increased.
Digoxin	Digoxin: Plasma concentrations may be increased due to P-glycoprotein inhibition by Kaletra. The increased digoxin level may lessen over time as Pgp induction develops.	Caution is warranted and therapeutic drug monitoring of digoxin concentrations, if available, is recommended in case of co-administration of Kaletra and digoxin. Particular caution should be used when prescribing Kaletra in patients taking digoxin as the acute inhibitory effect of ritonavir on Pgp is expected to significantly increase digoxin levels. Initiation of digoxin in patients already taking Kaletra is likely to result in lower than expected increases of digoxin concentrations.
Bepridil, Systemic Lidocaine, and Quinidine	Bepridil, Systemic Lidocaine, Quinidine: Concentrations may be increased when co-administered with Kaletra.	Caution is warranted and therapeutic drug concentration monitoring is recommended when available.
Antibiotics		
Clarithromycin	Clarithromycin: Moderate increases in clarithromycin AUC are expected due to CYP3A inhibition by Kaletra.	For patients with renal impairment (CrCL < 30 ml/min) dose reduction of clarithromycin should be considered (see section 4.4). Caution should be exercised in administering clarithromycin with Kaletra to patients with impaired hepatic or renal function.
Anticancer agents		
Afatinib (Ritonavir 200 mg twice daily)	Afatinib: AUC: ↑ Cmax: ↑ The extent of increase depends on the timing of ritonavir administration. Due to BCRP (breast cancer resistance protein/ABCG2) and acute P-gp inhibition by Kaletra	Caution should be exercised in administering afatinib with Kaletra. Refer to the afatinib SmPC for dosage adjustment recommendations. Monitor for ADRs related to afatinib.
Ceritinib	Serum concentrations may be increased due to CYP3A and P-gp inhibition by Kaletra.	Caution should be exercised in administering ceritinib with Kaletra. Refer to the ceritinib SmPC for dosage

		adjustment recommendations. Monitor for ADRs related to ceritinib.
Most tyrosine kinase inhibitors such as dasatinib and nilotinib, vincristine, vinblastine	Most tyrosine kinase inhibitors such as dasatinib and nilotinib, also vincristine and vinblastine: Risk of increased adverse events due to higher serum concentrations because of CYP3A4 inhibition by Kaletra.	Careful monitoring of the tolerance of these anticancer agents.
Anticoagulants		
Warfarin	Warfarin: Concentrations may be affected when co-administered with Kaletra due to CYP2C9 induction.	It is recommended that INR (international normalised ratio) be monitored.
Rivaroxaban (Ritonavir 600 mg twice daily)	Rivaroxaban: AUC: ↑ 153% Cmax: ↑ 55% Due to CYP3A and P-gp inhibition by lopinavir/ritonavir.	Co-administration of rivaroxaban and Kaletra may increase rivaroxaban exposure which may increase the risk of bleeding. The use of rivaroxaban is not recommended in patients receiving concomitant treatment with Kaletra (see section 4.4).
Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by Kaletra.	The coadministration of vorapaxar with Kaletra is not recommended (see section 4.4 and refer to the vorapaxar SmPC).
Anticonvulsants		
Phenytoin	Phenytoin: Steady-state concentrations was moderately decreased due to CYP2C9 and CYP2C19 induction by Kaletra. Lopinavir: Concentrations are decreased due to CYP3A induction by phenytoin.	Caution should be exercised in administering phenytoin with Kaletra. Phenytoin levels should be monitored when co-administering with lopinavir/ritonavir. When co-administered with phenytoin, an increase of Kaletra dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. Kaletra must not be administered once daily in combination with phenytoin.
Carbamazepine and Phenobarbital	Carbamazepine: Serum concentrations may be increased due to CYP3A inhibition by Kaletra.	Caution should be exercised in administering carbamazepine or phenobarbital with Kaletra. Carbamazepine and phenobarbital levels

	Lopinavir: Concentrations may be decreased due to CYP3A induction by carbamazepine and phenobarbital.	should be monitored when co-administering with lopinavir/ritonavir. When co-administered with carbamazepine or phenobarbital, an increase of Kaletra dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. Kaletra must not be administered once daily in combination with carbamazepine and phenobarbital.
Lamotrigine and Valproate	Lamotrigine: AUC: ↓ 50% Cmax: ↓ 46% Cmin: ↓ 56% Due to induction of lamotrigine glucuronidation Valproate: ↓	Patients should be monitored closely for a decreased VPA effect when Kaletra and valproic acid or valproate are given concomitantly. In patients starting or stopping Kaletra while currently taking maintenance dose of lamotrigine: lamotrigine dose may need to be increased if Kaletra is added, or decreased if Kaletra is discontinued; therefore plasma lamotrigine monitoring should be conducted, particularly before and during 2 weeks after starting or stopping Kaletra, in order to see if lamotrigine dose adjustment is needed. In patients currently taking Kaletra and starting lamotrigine: no dose adjustments to the recommended dose escalation of lamotrigine should be necessary.
Antidepressants and Anxiolytics		
Trazodone single dose (Ritonavir, 200 mg BID)	Trazodone: AUC: ↑ 2.4-fold Adverse events of nausea, dizziness, hypotension and syncope were observed following co-administration of trazodone and ritonavir.	It is unknown whether the combination of lopinavir/ritonavir causes a similar increase in trazodone exposure. The combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals		
Ketoconazole and Itraconazole	Ketoconazole, Itraconazole: Serum concentrations may be increased due to CYP3A inhibition by Kaletra.	High doses of ketoconazole and itraconazole (> 200 mg/day) are not recommended.
Voriconazole	Voriconazole: Concentrations may be decreased.	Co-administration of voriconazole and low dose ritonavir (100 mg BID) as contained in Kaletra should be avoided unless an

		assessment of the benefit/risk to patient justifies the use of voriconazole.
Anti-gout agents		
Colchicine single dose (Ritonavir 200 mg twice-daily)	Colchicine: AUC: ↑ 3-fold Cmax: ↑ 1.8-fold Due to P-gp and/or CYP3A4 inhibition by ritonavir.	Concomitant administration of Kaletra with colchicine in patients with renal and/or hepatic impairment is contraindicated due to a potential increase of colchicine-related serious and/or life-threatening reactions such as neuromuscular toxicity (including rhabdomyolysis) (see sections 4.3 and 4.4). A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with Kaletra is required. Refer to colchicine prescribing information.
Anti-infectives		
Fusidic acid	Fusidic acid: Concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Concomitant administration of Kaletra with fusidic acid is contra-indicated in dermatological indications due to the increased risk of adverse events related to fusidic acid, notably rhabdomyolysis (see section 4.3). When used for osteo-articular infections, where the co-administration is unavoidable, close clinical monitoring for muscular adverse events is strongly recommended (see section 4.4).
Antimycobacterials		
Bedaquiline (single dose) (Lopinavir/ritonavir 400/100 mg BID, multiple dose)	Bedaquiline: AUC: ↑ 22% Cmax: ↔ A more pronounced effect on bedaquiline plasma exposures may be observed during prolonged co-administration with lopinavir/ritonavir. CYP3A4 inhibition likely due to lopinavir/ritonavir.	Due to the risk of bedaquiline related adverse events, the combination of bedaquiline and lopinavir/ritonavir should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with lopinavir/ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.4 and refer to the bedaquiline SmPC).
Delamanid (100 mg BID) (Lopinavir/ritonavir 400/100 mg BID)	Delamanid: AUC: ↑ 22% DM-6705 (delamanid active metabolite):	Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with lopinavir/ritonavir is considered necessary,

	AUC: ↑ 30% A more pronounced effect on DM-6705 exposure may be observed during prolonged co-administration with lopinavir/ritonavir.	very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid SmPC).
Rifabutin, 150 mg QD	Rifabutin (parent drug and active 25-O-desacetyl metabolite): AUC: ↑ 5.7-fold Cmax: ↑ 3.5-fold	When given with Kaletra the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for Kaletra.
Rifampicin	Lopinavir: Large decreases in lopinavir concentrations may be observed due to CYP3A induction by rifampicin.	Co-administration of Kaletra with rifampicin is not recommended as the decrease in lopinavir concentrations may in turn significantly decrease the lopinavir therapeutic effect. A dose adjustment of Kaletra 400 mg/400 mg (i.e. Kaletra 400/100 mg + ritonavir 300 mg) twice daily has allowed compensating for the CYP 3A4 inducer effect of rifampicin. However, such a dose adjustment might be associated with ALT/AST elevations and with increase in gastrointestinal disorders. Therefore, this co-administration should be avoided unless judged strictly necessary. If this co-administration is judged unavoidable, increased dose of Kaletra at 400 mg/400 mg twice daily may be administered with rifampicin under close safety and therapeutic drug monitoring. The Kaletra dose should be titrated upward

		only after rifampicin has been initiated (see section 4.4).
Antipsychotics		
Lurasidone	Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of lurasidone are expected to increase.	The concomitant administration with lurasidone is contraindicated (see section 4.3).
Quetiapine	Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase.	Concomitant administration of Kaletra and quetiapine is contraindicated as it may increase quetiapine-related toxicity.
Benzodiazepines		
Midazolam	Oral Midazolam: AUC: ↑ 13-fold Parenteral Midazolam: AUC: ↑ 4-fold Due to CYP3A inhibition by Kaletra	Kaletra must not be co-administered with oral midazolam (see section 4.3), whereas caution should be used with co-administration of Kaletra and parenteral midazolam. If Kaletra is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered especially if more than a single dose of midazolam is administered.
Beta2-adrenoceptor agonist (long acting)		
Salmeterol	Salmeterol: Concentrations are expected to increase due to CYP3A inhibition by lopinavir/ritonavir.	The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Therefore, concomitant administration of Kaletra with salmeterol is not recommended (see section 4.4).
Calcium channel blockers		
Felodipine, Nifedipine, and Nicardipine	Felodipine, Nifedipine, Nicardipine: Concentrations may be increased due to CYP3A inhibition by Kaletra.	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with Kaletra.
Corticosteroids		

Dexamethasone	Lopinavir: Concentrations may be decreased due to CYP3A induction by dexamethasone.	Clinical monitoring of antiviral efficacy is recommended when these medicines are concomitantly administered with Kaletra.
Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone	Fluticasone propionate, 50 mg intranasal 4 times daily: Plasma concentrations ↑ Cortisol levels ↓ 86%	Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide and triamcinolone. Consequently, concomitant administration of Kaletra and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period.
Phosphodiesterase(PDE5) inhibitors		
Avanafil (ritonavir 600 mg BID)	Avanafil: AUC: ↑ 13-fold Due to CYP3A inhibition by lopinavir/ritonavir.	The use of avanafil with Kaletra is contraindicated (see section 4.3).
Tadalafil	Tadalafil: AUC: ↑ 2-fold Due to CYP3A4 inhibition by lopinavir/ritonavir.	For the treatment of pulmonary arterial hypertension: Co-administration of Kaletra with sildenafil is contraindicated (see section 4.3). Co-administration of Kaletra with tadalafil is not recommended. For erectile dysfunction: Particular caution must be used when prescribing sildenafil or tadalafil in patients receiving Kaletra with increased monitoring for adverse events including hypotension, syncope, visual changes and
Sildenafil	Sildenafil: AUC: ↑ 11-fold Due to CYP3A inhibition by lopinavir/ritonavir.	

		prolonged erection (see section 4.4). When co-administered with Kaletra, sildenafil doses must not exceed 25 mg in 48 hours and tadalafil doses must not exceed 10 mg every 72 hours.
Vardenafil	Vardenafil: AUC: ↑ 49-fold Due to CYP3A inhibition by Kaletra.	The use of vardenafil with Kaletra is contraindicated (see section 4.3).
HCV Protease Inhibitors		
Boceprevir 800 mg three times daily	Boceprevir: AUC: ↓ 45% Cmax: ↓ 50% Cmin: ↓ 57% Lopinavir: AUC: ↓ 34% Cmax: ↓ 30% Cmin: ↓ 43%	It is not recommended to co-administer Kaletra and boceprevir.
Simeprevir 200 mg daily (ritonavir 100 mg BID)	Simeprevir: AUC: ↑ 7.2-fold Cmax: ↑ 4.7-fold Cmin: ↑ 14.4-fold	It is not recommended to co-administer Kaletra and simeprevir.
Telaprevir 750 mg three times daily	Telaprevir: AUC: ↓ 54% Cmax: ↓ 53% Cmin: ↓ 52% Lopinavir: ↔	It is not recommended to co-administer Kaletra and telaprevir.
Herbal products		
St John's wort (Hypericum perforatum)	Lopinavir: Concentrations may be reduced due to induction of CYP3A by the herbal preparation St John's wort.	Herbal preparations containing St John's wort must not be combined with lopinavir and ritonavir. If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Lopinavir and ritonavir levels may increase on stopping St John's wort. The dose of Kaletra may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort (see section 4.3). Therefore, Kaletra can be started safely 2 weeks after cessation of St John's wort.
Immunosuppressants		

Cyclosporin, Sirolimus (rapamycin), and Tacrolimus	Cyclosporin, Sirolimus (rapamycin), Tacrolimus: Concentrations may be increased due to CYP3A inhibition by Kaletra.	More frequent therapeutic concentration monitoring is recommended until plasma levels of these products have been stabilised.
Lipid lowering agents		
Lovastatin and Simvastatin	Lovastatin, Simvastatin: Markedly increased plasma concentrations due to CYP3A inhibition by Kaletra.	Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these agents with Kaletra is contraindicated (see section 4.3).
Atorvastatin	Atorvastatin: AUC: ↑ 5.9-fold Cmax: ↑ 4.7-fold Due to CYP3A inhibition by Kaletra.	The combination of Kaletra with atorvastatin is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring (see section 4.4).
Rosuvastatin, 20 mg QD	Rosuvastatin: AUC: ↑ 2-fold Cmax: ↑ 5-fold While rosuvastatin is poorly metabolised by CYP3A4, an increase of its plasma concentrations was observed. The mechanism of this interaction may result from inhibition of transport proteins.	Caution should be exercised and reduced doses should be considered when Kaletra is co-administered with rosuvastatin (see section 4.4).
Fluvastatin or Pravastatin	Fluvastatin, Pravastatin: No clinical relevant interaction expected. Pravastatin is not metabolised by CYP450. Fluvastatin is partially metabolised by CYP2C9.	If treatment with an HMG-CoA reductase inhibitor is indicated, fluvastatin or pravastatin is recommended.
Opioids		
Buprenorphine, 16 mg QD	Buprenorphine: ↔	No dose adjustment necessary.
Methadone	Methadone: ↓	Monitoring plasma concentrations of methadone is recommended.
Oral Contraceptives		
Ethinyl Oestradiol	Ethinyl Oestradiol: ↓	In case of co-administration of Kaletra

		with contraceptives containing ethinyl oestradiol (whatever the contraceptive formulation e.g. oral or patch), additional methods of contraception must be used.
Smoking cessation aids		
Bupropion	Buproprion and its active metabolite, hydroxybupropion: AUC and Cmax ↓ ~50% This effect may be due to induction of bupropion metabolism.	If the co-administration of lopinavir/ritonavir with bupropion is judged unavoidable, this should be done under close clinical monitoring for bupropion efficacy, without exceeding the recommended dosage, despite the observed induction.
Vasodilating agents		
Bosentan	Lopinavir - ritonavir: Lopinavir/ritonavir plasma concentrations may decrease due to CYP3A4 induction by bosentan. Bosentan: AUC: ↑ 5-fold Cmax: ↑ 6-fold Initially, bosentan Cmin :↑ by approximately 48-fold. Due to CYP3A4 inhibition by lopinavir/ritonavir.	Caution should be exercised in administering Kaletra with bosentan. When Kaletra is administered concomitantly with bosentan, the efficacy of the HIV therapy should be monitored and patients should be closely observed for bosentan toxicity, especially during the first week of co-administration.
Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by Kaletra.	The coadministration of riociguat with Kaletra is not recommended (see section 4.4 and refer to riociguat SmPC).
Other medicinal products		
Based on known metabolic profiles, clinically significant interactions are not expected between Kaletra and dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole.		

4.6 Pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus.

Lopinavir/ritonavir has been evaluated in over 3000 women during pregnancy, including over

1000 during the first trimester.

In post-marketing surveillance through the Antiretroviral Pregnancy Registry, established since January 1989, an increased risk of birth defects exposures with Lopinavir and Ritonavir has not been reported among over 1000 women exposed during 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 etiology was seen. Studies in animals have shown reproductive toxicity (see section 5.3). Based on the data mentioned, the malformative risk is unlikely in humans. Lopinavir can be used during pregnancy if clinically needed.

Lactation

Studies in rats revealed that lopinavir is excreted in the milk. It is not known whether this medicinal product is excreted in human milk. As a general rule, it is recommended that mothers infected by HIV do not breastfeed their babies under any circumstances in order to avoid transmission of HIV.

Fertility

Animal studies have shown no effects on fertility. No human data on the effect of lopinavir/ritonavir on fertility are available.

4.7 Effects on ability to drive and use machine.

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 Lopinavir and Ritonavir (see section 4.8).

4.8 Undesirable effect.

Summary of the safety profile

The safety of Lopinavir and Ritonavir has been investigated in over 2600 patients in Phase II-IV clinical trials, of which over 700 have received a dose of 800/200 mg (6 capsules or 4 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies, Lopinavir and Ritonavir was used in combination with efavirenz or nevirapine.

The most common adverse reactions related to Lopinavir and Ritonavir therapy during clinical

trials were diarrhoea, nausea, vomiting, hypertriglyceridaemia and hypercholesterolemia. The risk of diarrhoea may be greater with once-daily dosing of Lopinavir and Ritonavir Diarrhoea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridaemia and hypercholesterolemia may occur later. Treatment emergent adverse events led to premature study discontinuation for 7% of subjects from Phase II-IV studies.

It is important to note that cases of pancreatitis have been reported in patients receiving Lopinavir and Ritonavir, including those who developed hypertriglyceridaemia. Furthermore, rare increases in PR interval have been reported during Lopinavir and Ritonavir therapy (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions from clinical trials and post-marketing experience in adult and paediatric patients:

The following events have been identified as adverse reactions. The frequency category includes all reported events of moderate to severe intensity, regardless of the individual causality assessment. The adverse reactions are displayed by system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and not known (cannot be estimated from the available data).

Events noted as having frequency "Not known" were identified via post-marketing surveillance.

Undesirable effects in clinical studies and post-marketing in adult patients		
System organ class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection
	Common	Lower respiratory tract infection, skin infections including cellulitis, folliculitis and furuncle
Blood and lymphatic system disorders	Common	Anaemia, leucopenia, neutropenia, lymphadenopathy
Immune system disorders	Common	Hypersensitivity including urticaria and angioedema
	Uncommon	Immune reconstitution inflammatory syndrome
Endocrine disorders	Uncommon	Hypogonadism
Metabolism and nutrition disorders	Common	Blood glucose disorders including diabetes mellitus, hypertriglyceridaemia,

		hypercholesterolemia, weight decreased, decreased appetite
	Uncommon	Weight increased, increased appetite
Psychiatric disorders	Common	Anxiety
	Uncommon	Abnormal dreams, libido decreased
Nervous system disorders	Common	Headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, insomnia
	Uncommon	Cerebrovascular accident, convulsion, dysgeusia, ageusia, tremor
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Tinnitus, vertigo
Cardiac disorders	Uncommon	Atherosclerosis such as myocardial infarction, atrioventricular block, tricuspid valve incompetence
Vascular disorders	Common	Hypertension
	Uncommon	Deep vein thrombosis
Gastrointestinal disorders	Very common	Diarrhoea, nausea
	Common	Pancreatitis1, vomiting, gastrooesophageal reflux disease, gastroenteritis and colitis, abdominal pain (upper and lower), abdominal distension, dyspepsia, haemorrhoids, flatulence
	Uncommon	Gastrointestinal haemorrhage including gastrointestinal ulcer, duodenitis, gastritis and rectal haemorrhage, stomatitis and oral ulcers, faecal incontinence, constipation, dry mouth
Hepatobiliary disorders	Common	Hepatitis including AST, ALT and GGT increases
	Uncommon	Hepatic steatosis, hepatomegaly, cholangitis, hyperbilirubinemia
	Not known	Jaundice
Skin and subcutaneous tissue disorders	Common	Rash including maculopapular rash, dermatitis/rash including eczema and seborrheic dermatitis, night sweats, pruritus
	Uncommon	Alopecia, capillaritis, vasculitis
	Not known	Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	Common	Myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such

		as weakness and spasms
	Uncommon	Rhabdomyolysis, osteonecrosis
Renal and urinary disorders	Uncommon	Creatinine clearance decreased, nephritis, haematuria
Reproductive system and breast disorders	Common	Erectile dysfunction, menstrual disorders - amenorrhoea, menorrhagia
General disorders and administration site conditions	Common	Fatigue including asthenia

1 See section 4.4: pancreatitis and lipids

Description of selected adverse reactions

Cushing's syndrome has been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide (see section 4.4 and 4.5).

Increased creatine phosphokinase (CPK), myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Paediatric population

In children 2 years of age and older, the nature of the safety profile is similar to that seen in adults (see Table in section b).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the authority ADR reporting tool; search for authority Adverse Reactions Reporting Tool in the Google Play Store.

4.9 Overdose

To date, there is limited human experience of acute overdose with Lopinavir and Ritonavir

The adverse clinical signs observed in dogs included salivation, emesis and diarrhoea/abnormal stool. The signs of toxicity observed in mice, rats or dogs included decreased activity, ataxia, emaciation, dehydration and tremors.

There is no specific antidote for overdose with Lopinavir and Ritonavir Treatment of overdose with Lopinavir and Ritonavir is to consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since Lopinavir and Ritonavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

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 provides the antiviral activity of Lopinavir and Ritonavir. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus.

Effects on the electrocardiogram

QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on

Day 3. The maximum mean (95% upper confidence bound) differences in QTcF from placebo were 3.6 (6.3) and 13.1(15.8) for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily LPV/r, respectively. The induced QRS interval prolongation from 6 ms to 9.5 ms with high dose lopinavir/ritonavir (800/200 mg twice daily) contributes to QT prolongation. The two regimens resulted in exposures on Day 3 which were approximately 1.5 and 3-fold higher than those observed with recommended once-daily or twice-daily LPV/r 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. The mean changes from baseline in PR interval ranged from 11.6 ms to 24.4 ms in the 12 hour interval post dose. Maximum PR interval was 286 msec and no second or third degree heart block was observed (see section 4.4).

Antiviral Activity in vitro

The in vitro antiviral activity of lopinavir against laboratory and clinical HIV strains was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean IC50 of lopinavir against five different HIV-1 laboratory strains was 19 nM. In the absence and presence of 50% human serum, the mean IC50 of lopinavir against HIV-1IIIB in MT4 cells was 17 nM and 102 nM, respectively. In the absence of human serum, the mean IC50 of lopinavir was 6.5 nM against several HIV-1 clinical isolates.

Resistance

In vivo resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected in vitro. HIV-1 has been passaged in vitro with lopinavir alone and with lopinavir plus ritonavir at concentration ratios representing the range of plasma concentration ratios observed during Lopinavir and Ritonavir therapy. Genotypic and phenotypic analysis of viruses selected in these passages suggest that the presence of ritonavir, at these concentration ratios, does not measurably influence the selection of lopinavir-resistant viruses. Overall, the in vitro characterisation of phenotypic cross-resistance between lopinavir and other protease inhibitors suggest that decreased susceptibility to lopinavir correlated closely with decreased susceptibility to ritonavir

and indinavir, but did not correlate closely with decreased susceptibility to amprenavir, saquinavir, and nelfinavir.

Analysis of resistance in ARV-naïve patients

In clinical studies with a limited number of isolates analysed, the selection of resistance to lopinavir has not been observed in naïve patients without significant protease inhibitor resistance at baseline. See further the detailed description of the clinical studies.

Analysis of resistance in PI-experienced patients

The selection of resistance to lopinavir in patients having failed prior protease inhibitor therapy was characterised by analysing the longitudinal isolates from 19 protease inhibitor-experienced subjects in 2 Phase II and one Phase III studies who either experienced incomplete virologic suppression or viral rebound subsequent to initial response to Lopinavir and Ritonavir and who demonstrated incremental in vitro resistance between baseline and rebound (defined as emergence of new mutations or 2-fold change in phenotypic susceptibility to lopinavir). Incremental resistance was most common in subjects whose baseline isolates had several protease inhibitor-associated mutations, but < 40-fold reduced susceptibility to lopinavir at baseline. Mutations V82A, I54V and M46I emerged most frequently. Mutations L33F, I50V and V32I combined with I47V/A were also observed. The 19 isolates demonstrated a 4.3-fold increase in IC50 compared to baseline isolates (from 6.2- to 43-fold, compared to wild-type virus).

Genotypic correlates of reduced phenotypic susceptibility to lopinavir in viruses selected by other protease inhibitors. The in vitro antiviral activity of lopinavir against 112 clinical isolates taken from patients failing therapy with one or more protease inhibitors was assessed. Within this panel, the following mutations in HIV protease were associated with reduced in vitro susceptibility to lopinavir: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M. The median EC50 of lopinavir against isolates with 0 − 3, 4 − 5, 6 − 7 and 8 − 10 mutations at the above amino acid positions was 0.8, 2.7 13.5 and 44.0-fold higher than the EC50 against wild type HIV, respectively. The 16 viruses that displayed > 20-fold change in susceptibility all contained mutations at positions 10, 54, 63 plus 82 and/or 84. In addition, they contained a median of 3 mutations at amino acid positions 20, 24, 46, 53, 71 and 90. In addition to the mutations described above, mutations V32I and I47A have

been observed in rebound isolates with reduced lopinavir susceptibility from protease inhibitor experienced patients receiving Kaletra therapy, and mutations I47A and L76V have been observed in rebound isolates with reduced lopinavir susceptibility from patients receiving Lopinavir and Ritonavir therapy.

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

Antiviral activity of Lopinavir and Ritonavir in patients failing 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 patients previous failing therapy with multiple protease inhibitors. The EC50 of lopinavir against the 56 baseline viral isolates ranged from 0.6 to 96-fold higher than the EC50 against wild type HIV. After 48 weeks of treatment with Kaletra, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA ≤ 400 copies/ml was observed in 93% (25/27), 73% (11/15), and 25% (2/8) of patients with < 10-fold, 10 to 40-fold, and > 40-fold reduced susceptibility to lopinavir at baseline, respectively. In addition, virologic response was observed in 91% (21/23), 71% (15/21) and 33% (2/6) patients with 0 − 5, 6 − 7, and 8 − 10 mutations of the above mutations in HIV protease associated with reduced in vitro susceptibility to lopinavir. Since these patients had not previously been exposed to either Kaletra or efavirenz, part of the response may be attributed to the antiviral activity of efavirenz, particularly in patients harbouring highly lopinavir resistant virus. The study did not contain a control arm of patients not receiving Lopinavir and Ritonavir

cross-resistance

Activity of other protease inhibitors against isolates that developed incremental resistance to lopinavir after Kaletra therapy in protease inhibitor experienced patients: The presence of cross resistance to other protease inhibitors was analysed in 18 rebound isolates that had demonstrated evolution of resistance to lopinavir during 3 Phase II and one Phase III studies of Lopinavir and Ritonavir in protease inhibitor-experienced patients. The median fold IC50 of lopinavir for these 18 isolates at baseline and rebound was 6.9- and 63-fold, respectively, compared to wild type virus. In general, rebound isolates either retained (if cross-resistant at baseline) or developed

significant cross-resistance to indinavir, saquinavir and atazanavir. Modest decreases in amprenavir activity were noted with a median increase of IC50 from 3.7- to 8-fold in the baseline and rebound isolates, respectively. Isolates retained susceptibility to tipranavir with a median increase of IC50 in baseline and rebound isolates of 1.9- and 1.8–fold, respectively, compared to wild type virus. Please refer to the Aptivus Summary of Product Characteristics for additional information on the use of tipranavir, including genotypic predictors of response, in treatment of lopinavir-resistant HIV-1 infection.

Clinical results

The effects of Lopinavir and Ritonavir (in combination with other antiretroviral agents) on biological markers (plasma HIV RNA levels and CD4+ T-cell counts) have been investigated in controlled studies of Lopinavir and Ritonavir of 48 to 360 weeks duration.

Adult Use

Patients without prior antiretroviral therapy

Study M98-863 was a randomised, double-blind trial of 653 antiretroviral treatment naïve patients investigating Lopinavir and Ritonavir (400/100 mg twice daily) compared to nelfinavir (750 mg three times daily) plus stavudine and lamivudine. Mean baseline CD4+ T-cell count was 259 cells/mm3 (range: 2 to 949 cells/ mm3) and mean baseline plasma HIV-1 RNA was 4.9 log10 copies/ml (range: 2.6 to 6.8 log10 copies/ml).

Table 1

Outcomes at Week 48: Study M98-863		
	Kaletra (N=326)	Nelfinavir (N=327)
HIV RNA < 400 copies/ml*	75%	63%
HIV RNA < 50 copies/ml*†	67%	52%
Mean increase from baseline in CD4+ T-cell count (cells/mm3)	207	195

* intent to treat analysis where patients with missing values are considered virologic failures

† $p < 0.001$

One-hundred thirteen nelfinavir-treated patients and 74 lopinavir/ritonavir-treated patients had an HIV RNA above 400 copies/ml while on treatment from Week 24 through Week 96. Of these,

isolates from 96 nelfinavir-treated patients and 51 lopinavir/ritonavir-treated patients could be amplified for resistance testing. Resistance to nelfinavir, defined as the presence of the D30N or L90M mutation in protease, was observed in 41/96 (43%) patients. Resistance to lopinavir, defined as the presence of any primary or active site mutations in protease (see above), was observed in 0/51 (0%) patients. Lack of resistance to lopinavir was confirmed by phenotypic analysis.

Study M05-730 was a randomised, open-label, multicentre trial comparing treatment with Lopinavir and Ritonavir 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. Given the pharmacokinetic interaction between Lopinavir and Ritonavir and tenofovir (see section 4.5), the results of this study might not be strictly extrapolable when other backbone regimens are used with Lopinavir and Ritonavir. Patients were randomised in a 1:1 ratio to receive either Lopinavir and Ritonavir 800/200 mg once daily (n = 333) or Lopinavir and Ritonavir 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. Protocol defined non-inferiority of once-daily dosing compared with twice-daily dosing was demonstrated if the lower bound of the 95% confidence interval for the difference in proportion of subjects responding (once daily minus twice daily) excluded -12% at Week 48. Mean age of patients enrolled was 39 years (range: 19 to 71); 75% were Caucasian, and 78% were male. Mean baseline CD4+ T-cell count was 216 cells/mm3 (range: 20 to 775 cells/mm3) and mean baseline plasma HIV-1 RNA was 5.0 log10 copies/ml (range: 1.7 to 7.0 log10 copies/ml).

Table 2

Virologic Response of Study Subjects at Week 48 and Week 96						
	Week 48			Week 96		
	QD	BID	Difference [95% CI]	QD	BID	Difference [95% CI]
NC= Failure	257/333 (77.2%)	251/331 (75.8%)	1.3 % [-5.1, 7.8]	216/333 (64.9%)	229/331 (69.2%)	-4.3% [-11.5, 2.8]

Observed data	257/295 (87.1%)	250/280 (89.3%)	-2.2% [-7.4, 3.1]	216/247 (87.4%)	229/248 (92.3%)	-4.9% [-10.2, 0.4]
Mean increase from baseline in CD4+ T-cell count (cells/mm3)	186	198		238	254	

Through Week 96, genotypic resistance testing results were available from 25 patients in the QD group and 26 patients in the BID group who had incomplete virologic response. In the QD group, no patient demonstrated lopinavir resistance, and in the BID group, 1 patient who had significant protease inhibitor resistance at baseline demonstrated additional lopinavir resistance on study.

Sustained virological response to Lopinavir and Ritonavir (in combination with nucleoside/nucleotide reverse transcriptase inhibitors) has been also observed in a small Phase II study (M97-720) through 360 weeks of treatment. One hundred patients were originally treated with Lopinavir and Ritonavir in the study (including 51 patients receiving 400/100 mg twice daily and 49 patients at either 200/100 mg twice daily or 400/200 mg twice daily). All patients converted to open-label Lopinavir and Ritonavir at the 400/100 mg twice-daily dose between week 48 and week 72. Thirty-nine patients (39%) discontinued the study, including 16 (16%) discontinuations due to adverse events, one of which was associated with a death. Sixty-one patients completed the study (35 patients received the recommended 400/100 mg twice-daily dose throughout the study).

Table 3

Outcomes at Week 360: Study M97-720	
	Kaletra (N=100)
HIV RNA < 400 copies/ml	61%
HIV RNA < 50 copies/ml	59%
Mean increase from baseline in CD4+ T-cell count (cells/mm3)	501

Through 360 weeks of treatment, genotypic analysis of viral isolates was successfully conducted in 19 of 28 patients with confirmed HIV RNA above 400 copies/ml revealed no primary or active site mutations in protease (amino acids at positions 8, 30, 32, 46, 47, 48, 50, 82, 84 and 90) or protease inhibitor phenotypic resistance.

Patients with prior antiretroviral therapy

M06-802 was a randomised open-label study comparing the safety, tolerability and antiviral activity of once-daily and twice-daily dosing of lopinavir/ritonavir tablets in 599 subjects with detectable viral loads while receiving their current antiviral therapy. Patients had not been on prior lopinavir/ritonavir therapy. They were randomised in a 1:1 ratio to receive either lopinavir/ritonavir 800/200 mg once daily (n = 300) or lopinavir/ritonavir 400/100 mg twice daily (n = 299). Patients were administered at least two nucleoside/nucleotide reverse transcriptase inhibitors selected by the investigator. The enrolled population was moderately PI-experienced with more than half of patients having never received prior PI and around 80% of patients presenting a viral strain with less than 3 PI mutations. Mean age of patients enrolled was 41 years (range: 21 to 73); 51% were Caucasian and 66% were male. Mean baseline CD4+ T-cell count was 254 cells/mm3 (range: 4 to 952 cells/mm3) and mean baseline plasma HIV-1 RNA was 4.3 log10 copies/ml (range: 1.7 to 6.6 log10 copies/ml). Around 85% of patients had a viral load of < 100,000 copies/ml.

Table 4

Virologic Response of Study Subjects at Week 48 Study 802			
	QD	BID	Difference [95% CI]
NC= Failure	171/300 (57%)	161/299 (53.8%)	3.2% [-4.8%, 11.1%]
Observed data	171/225 (76.0%)	161/223 (72.2%)	3.8% [-4.3%, 11.9%]
Mean increase from baseline in CD4+ T-cell count (cells/mm3)	135	122	

Through Week 48, genotypic resistance testing results were available from 75 patients in the QD group and 75 patients in the BID group who had incomplete virologic response. In the QD group, 6/75 (8%) patients demonstrated new primary protease inhibitor mutations (codons 30, 32, 48, 50, 82, 84, 90), as did 12/77 (16%) patients in the BID group.

Paediatric Use

M98-940 was an open-label study of a liquid formulation of Lopinavir and Ritonavir 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 m2 or 300 mg lopinavir/75 mg ritonavir per m2. Naïve patients

also received nucleoside reverse transcriptase inhibitors. 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 3 weeks of therapy in each patient. Subsequently, all patients were continued on the 300/75 mg per m2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14 patients less than 2 years old and 6 patients one year or less. Mean baseline CD4+ T-cell count was 838 cells/mm3 and mean baseline plasma HIV-1 RNA was 4.7 log10 copies/ml.

Table 5

Outcomes at Week 48: Study M98-940		
	Antiretroviral Naïve (N=44)	Antiretroviral Experienced (N=56)
HIV RNA < 400 copies/ml	84%	75%
Mean increase from baseline in CD4+ T-cell count (cells/mm3)	404	284

KONCERT/PENTA 18 is a prospective multicentre, randomised, open-label study that evaluated the pharmacokinetic profile, efficacy and safety of twice-daily versus once-daily dosing of lopinavir/ritonavir 100 mg/25 mg tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged <18 years, ≥15 kg in weight, receiving cART that included lopinavir/ritonavir, HIV-1 ribonucleic acid (RNA) <50 copies/ml for at least 24 weeks and able to swallow tablets. At week 48, the efficacy and safety with twice-daily dosing (n=87) in the paediatric population given lopinavir/ritonavir 100 mg/25 mg tablets was consistent with the efficacy and safety findings in previous adult and paediatric studies using lopinavir/ritonavir twice daily. The percentage of patients with confirmed viral rebound >50 copies/ml during 48 weeks of follow-up was higher in the paediatric patients receiving lopinavir/ritonavir tablets once daily (12%) than in patients receiving the twice-daily dosing (8%, p = 0.19), mainly due to lower adherence in the once-daily group. The efficacy data favouring the twice-daily regimen are reinforced by a differential in pharmacokinetic parameters significantly favouring the twice-daily regimen (see section 5.2).

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 Lopinavir and Ritonavir 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 EC50 of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Kaletra is due to lopinavir.

Absorption

Multiple dosing with 400/100 mg Lopinavir and Ritonavir twice daily for 2 weeks and without meal restriction produced a mean ± SD lopinavir peak plasma concentration (Cmax) 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. 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 Lopinavir and Ritonavir tablets under fed conditions (high fat, 872 kcal, 56% from fat) compared to fasted state was associated with no significant changes in Cmax and AUCinf. Therefore, Kaletra tablets may be taken with or without food. Kaletra tablets have also shown less pharmacokinetic variability under all meal conditions compared to Kaletra soft capsules.

Distribution

At steady state, lopinavir is approximately 98 − 99% bound to serum 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 Lopinavir and Ritonavir 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 isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir and therefore, increases plasma levels of lopinavir. A 14C-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. The 4-oxo and 4-hydroxymetabolite epimeric pair are the major metabolites with antiviral activity, but comprise only minute amounts of total plasma radioactivity. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and likely the induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 days to 2 weeks.

Elimination

After a 400/100 mg 14C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of 14C-lopinavir can be accounted for in urine and faeces, respectively. 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 effective (peak to trough) half-life of lopinavir over a 12 hour dosing interval averaged 5 − 6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 l/h.

Once-daily dosing: the pharmacokinetics of once daily Lopinavir and Ritonavir have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Lopinavir and Ritonavir 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 Lopinavir and Ritonavir once daily for 2 weeks without meal restriction (n=16) produced a mean ± SD lopinavir peak plasma concentration (Cmax) 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. Lopinavir AUC over a 24 hour dosing interval averaged 206.5 ± 89.7 µg•h/ml.

As compared to the BID regimen, the once-daily dosing is associated with a reduction in the

Cmin/Ctrough values of approximately 50%.

Special Populations

Paediatrics

There are limited pharmacokinetic data in children below 2 years of age. The pharmacokinetics of Lopinavir and Ritonavir oral solution 300/75 mg/m2 twice daily and 230/57.5 mg/m2 twice daily have been studied in a total of 53 paediatric patients, ranging in age from 6 months to 12 years. The lopinavir mean steady-state AUC, Cmax, and Cmin were 72.6 ± 31.1 μg•h/ml, 8.2 ± 2.9 μg/ml and 3.4 ± 2.1 μg/ml, respectively after Lopinavir and Ritonavir oral solution 230/57.5 mg/m2 twice daily without nevirapine (n=12), and were 85.8 ± 36.9 μg•h/ml, 10.0 ± 3.3 μg/ml and 3.6 ± 3.5 μg/ml, respectively after 300/75 mg/m2 twice daily with nevirapine (n=12). The 230/57.5 mg/m2 twice-daily regimen without nevirapine and the 300/75 mg/m2 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.

Gender, Race and Age

Lopinavir and Ritonavir pharmacokinetics have not been studied in older people. No age or gender related pharmacokinetic differences have been observed in adult patients. Pharmacokinetic differences due to race have not been identified.

Pregnancy and postpartum

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. Plasma concentrations of lopinavir were measured over four 12-hour periods during second trimester (20-24 weeks gestation), third trimester before dose increase (30 weeks gestation), third trimester after dose increase (32 weeks gestation), and at 8 weeks post-partum. The dose increase did not result in a significant increase in the plasma lopinavir concentration.

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. A series of blood samples were collected pre-dose and at

intervals over the course of 12 hours in trimester 2 and trimester 3, at birth, and 4–6 weeks postpartum (in women who continued treatment post-delivery) for pharmacokinetic analysis of total and unbound levels of plasma lopinavir concentrations.

The pharmacokinetic data from HIV-1 infected pregnant women receiving lopinavir/ritonavir tablets 400/100 mg twice daily are presented in Table 6 (see section 4.2).

Table 6

Mean (%CV) Steady-State Pharmacokinetic Parameters of Lopinavir in HIV-Infected Pregnant Women			
Pharmacokinetic Parameter	2nd Trimester n = 17*	3rd Trimester n = 23	Postpartum n = 17**
AUC0-12 µg•hr/mL	68.7 (20.6)	61.3 (22.7)	94.3 (30.3)
Cmax	7.9 (21.1)	7.5 (18.7)	9.8 (24.3)
Cpredose µg /mL	4.7 (25.2)	4.3 (39.0)	6.5 (40.4)
* n = 18 for Cmax ** n = 16 for Cpredose			

Renal Insufficiency

Lopinavir and Ritonavir 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 Insufficiency

The steady state pharmacokinetic parameters of lopinavir in HIV-infected patients with mild to moderate hepatic impairment were compared with those of HIV-infected patients with normal hepatic function in a multiple dose study with lopinavir/ritonavir 400/100 mg twice daily. A limited increase in total lopinavir concentrations of approximately 30% has been observed which is not expected to be of clinical relevance (see section 4.2).

5.3 Preclinical safety data

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 or below 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

thyroxin 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 other species. Serum cholesterol was elevated in rodents but not dogs, while triglycerides were elevated only in mice.

During in vitro studies, cloned human cardiac potassium channels (HERG) were inhibited by 30% at the highest concentrations of lopinavir/ritonavir tested, corresponding to a lopinavir exposure 7-fold total and 15-fold free peak plasma levels achieved in humans at the maximum recommended therapeutic dose. In contrast, similar concentrations of lopinavir/ritonavir demonstrated no repolarisation delay in the canine cardiac Purkinje fibres. Lower concentrations of lopinavir/ritonavir did not produce significant potassium (HERG) current blockade. Tissue distribution studies conducted in the rat did not suggest significant cardiac retention of the active substance; 72-hour AUC in heart was approximately 50% of measured plasma AUC. Therefore, it is reasonable to expect that cardiac lopinavir levels would not be significantly higher than plasma levels.

In dogs, prominent U waves on the electrocardiogram have been observed associated with prolonged PR interval and bradycardia. These effects have been assumed to be caused by electrolyte disturbance.

The clinical relevance of these preclinical data is unknown, however, the potential cardiac effects of this product in humans cannot be ruled out (see also sections 4.4 and 4.8).

In rats, embryofoetotoxicity (pregnancy loss, decreased foetal viability, decreased foetal body weights, increased frequency of skeletal variations) and postnatal developmental toxicity (decreased survival of pups) was observed at maternally toxic dosages. The systemic exposure to lopinavir/ritonavir at the maternal and developmental toxic dosages was lower than the intended therapeutic exposure in humans.

Long-term carcinogenicity studies of lopinavir/ritonavir in mice revealed a nongenotoxic, mitogenic induction of liver tumours, generally considered to have little relevance to human risk. Carcinogenicity studies in rats revealed no tumourigenic findings. Lopinavir/ritonavir was not found to be mutagenic or clastogenic in a battery of in vitro and in vivo assays including the

Ames bacterial reverse mutation assay, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet contents: Copovidone**,** Sorbitan laurate, Colloidal anhydrous silica**,** Sodium stearyl fumarate

Film-coating: Hypromellose**,** Titanium dioxide**,** Macrogols type 400 (Polyethylene glycol 400)**,** Hydroxypropyl cellulose**,** Talc, Colloidal anhydrous silica**,** Macrogols type 3350 (Polyethylene glycol 3350)**,** Yellow ferric oxide E172**,** Polysorbate 80.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

200 mg/50 mg

Container: 120s HDPE Container

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

7.1 Name and Address of Applicant

Name : **M/s. Hetero Labs Limited,**

Business Address : 7-2-A2, Hetero Corporate,
Industrial Estates, Sanath Nagar,
Hyderabad-500 018
Telangana, INDIA

Telephone : +91-040-23704923/24/25

Fax : +91-040-23704926

7.2 Name and Address of Manufacturer

Name: Hetero Labs Limited (Unit-III)

Business Address: UNIT III, Survey No.: 51
22-110, Industrial Development Area,
Jeedimetla, Hyderabad,
PIN- 500 055, Telangana.
Country: INDIA
Phone: +91 40-23096171/172/173/174
Fax: +91 40-23095105