Summary of Product Characteristics

1. THE MEDICINAL PRODUCT
Lopinavir and Ritonavir oral granules 40 mg/10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains 40 mg lopinavir and 10 mg ritonavir. Each sachet contains 583 mg of mannitol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Granules for oral suspension
A white to creamish granular powder filled in a sachet.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications

Lopinavir/ Ritonavir oral granules is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in infants and children patients14 days and older, weighing over 3 kg.
The choice of Lopinavir/ Ritonavir oral granules to treat protease inhibitor-experienced HIV-1 infected patients should be based on individual viral resistance testing and their treatment history (see sections 4.4 and 5.1).

4.2. Posology and method of administration
Posology
Lopinavir/ Ritonavir oral granules should be initiated by a health care provider experienced in the management of HIV infection.

The recommended dose of Lopinavir/ Ritonavir oral granules for children is as follows:

Child's weight	Dose
3–5.9 kg	2 sachets twice daily (lopinavir 80 mg/ritonavir 20 mg twice daily)
6–9.9 kg	3 sachets twice daily (lopinavir 120 mg/ritonavir 30 mg twice daily)
10–13.9 kg	4 sachets twice daily (lopinavir 160 mg/ritonavir 40 mg twice daily)
14–19.9 kg	5 sachets twice daily (lopinavir 200 mg/ritonavir 50 mg twice daily)
20–24.9 kg	6 sachets twice daily (lopinavir 240 mg/ritonavir 60 mg twice daily)

For patients co-treated with nevirapine or efavirenz, see section 4.5.

Hepatic impairment
In HIV-infected patients with mild to moderate hepatic impairment, an approximate 30% increase 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/ Ritonavir Oral granules must not be given to thesepatients (see section 4.3).

Renal impairment
No dose adjustment is necessary in patients with renal impairment.Method of administration
For detail instructions on administration of Lopinavir/ Ritonavir Oral Granules, see section 6.6.

4.3. Contraindications
Hypersensitivity to the active substances or to any of the excipients.
Lopinavir/ Ritonavir Oral granules must not be administered to patients with severe hepatic impairment.

Lopinavir/ Ritonavir Oral granules must not be administered concurrently with agents with a narrow therapeutic window that are substrates of the isoenzyme CYP3A4, such as alfuzosin, amiodarone, dronedarone, bepridil, quinidine, propafenone, verapamil, lurasidone, pimozide, quetiapine, astemizole, terfenadine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ ritonavir (with or without dasabuvir), oral midazolam, triazolam, clorazepate, diazepam, flurazepam, ergot derivatives, fusidic acid, venetoclax, colchicine, simvastatin and lovastatin, avanafil, sildenafil and vardenafil (non-exhaustive list). Inhibition of CYP3A4 byritonavir could increase plasma concentrations of these agents, potentially causing serious or life-threateningreactions (see also sections 4.4 and 4.5).

Herbal preparations containing St John‟s wort (*Hypericum perforatum)* must not be used while taking lopinavir and ritonavir due to the risk of decreased plasma concentrations and reduced clinical effects oflopinavir and ritonavir (see section 4.5).

4.4. Special warnings and precautions for use

Patients with coexisting conditions
Hepatic impairment: Lopinavir/ Ritonavir Oral granules is contraindicated in patients with severe liver impairment. 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. For concomitant antiviral therapy for hepatitis B or C, refer to the relevant product information for these medicinal products.

Patients with liver dysfunction including chronic hepatitis have 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 oftreatment should be considered.
Laboratory tests should be conducted before starting treatment with lopinavir and ritonavir and duringtreatment.

Renal impairment: Since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Lopinavir and ritonavir are highly protein bound, therefore it is unlikely that they will be significantly removed by haemodialyis 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. A causal relationship is likely but a biological explanation has not been elucidated. Patients with haemophilia should therefore be warned of the possibility of increased bleeding.

Specific adverse reactions
Lipid elevations: Treatment with lopinavir and ritonavir has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol should be measured before starting Lopinavir/ Ritonavir oral granules and periodically during therapy. Particular caution should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders should be managed as clinically appropriate.

Pancreatitis: Cases of pancreatitis have been reported in patients receiving lopinavir and ritonavir. Most of these patients have had a history of pancreatitis 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 abnormal laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and Lopinavir/ Ritonavir oral granules therapy should be suspended if pancreatitis is diagnosed (see section 4.8).

Hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these cases hyperglycaemia was severe and also associated with ketoacidosis. Many patients had confounding medical conditions. A causal relation between ritonavir-boosted lopinavir and these events has not been established.
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.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency, typically in the first few weeks or months after initiation of combination antiretroviral treatment, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms.

Treatment should be instituted when necessary. Autoimmune disorders (such as Graves‟ disease) have also been reported in the setting of immune reactivation; 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. So far, this disorder has been reported mainly in adults. 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. Rarely, second- or third-degree atroventricular block has been reported in patients taking lopinavir/ritonavir who have underlying structural heart disease and conduction abnormalities or who are taking drugs that prolong the PR interval (such as verapamil or atazanavir). Lopinavir/ Ritonavir Oral granules should be used with caution in such patients (see sections 4.8, 5.1 and 5.3).

Warnings on specific interactions with other medicinal products
Lopinavir/ Ritonavir Oral granules contains ritonavir, which is a very potent inhibitor of the P450 isoform CYP3A. Lopinavir/ Ritonavir Oral granules 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).

Bedaquiline and delamanid: 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).

Rifampicin: Co-administration of Lopinavir/ Ritonavir Oral granules with rifampicin is not recommended. Rifampicin in combination with Lopinavir/ Ritonavir Oral granules causes large decreases in lopinavir concentrations which may in turn significantly decrease the therapeutic effect of lopinavir. Adequate exposure to lopinavir/ritonavir may be achieved with a higher dose of Lopinavir/ Ritonavir Oral granules but this is associated with a higher risk of liver and gastrointestinal toxicity.

HMG-CoA reductase inhibitors: Simvastatin and lovastatin are highly dependent on CYP3A for metabolism; thus concomitant use of Lopinavir/ Ritonavir Oral granules and simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if Lopinavir/ Ritonavir Oral granules is used concurrently with rosuvastatin or with atorvastatin, which are metabolised to a lesser extent by CYP3A4. 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/ Ritonavir Oral granules. Co-administration of Lopinavir/ Ritonavir Oral granules 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/ Ritonavir Oral granules is contraindicated (see section 4.3).

QT-interval prolonging agents: Particular caution must be used when prescribing Lopinavir/ Ritonavir Oral granules and medicinal products that prolong QT interval such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. Lopinavir/ Ritonavir Oral granules could increase concentrations of the coadministered medicinal products and this may increase their associated cardiac adverse events (see also section 4.3 and 4.5). Cardiac events have been reported with lopinavir/ritonavir in preclinical studies: therefore, potential cardiac effects of Lopinavir/ Ritonavir Oral granules cannot be currently ruled out (see sections 4.8 and 5.3).

Sedative agents: Lopinavir/ Ritonavir Oral granules should not be used concomitantly with strongly sedative drugs metabolized by CYP3A, as this may result in excessive effects. Such drugs include fentanyl, meperidine, propoxyphene, diazepam, alprazolam, triazolam and midazolam. Morphine and oxazepam are not metabolised by CYP3A; however, due to induction of glucuronidation, an increased dose of these drugs may be necessary when co-treating with Lopinavir/ Ritonavir Oral granules.

Hormonal contraceptives: In case of co-administration of Lopinavir/ Ritonavir Oral granules with contraceptives containing ethinylestradiol, irrespective of the formulation (e.g. oral or patch), additional barrier or non- hormonal methods of contraception are to be used. The decreased systemic exposure to the oestrogen component may not only reduce contraceptive efficacy but also alter the uterine bleeding profile.

Glucocorticoids: Concomitant use of Lopinavir/ Ritonavir Oral granules and fluticasone or other glucocorticoids that are metabolised by CYP3A4 such as budesonide and fluticasone, 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).
Colchicine: 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).

Tadalafil: Co-administration of Lopinavir/ Ritonavir Oral granules with tadalafil, indicated for the treatment of pulmonary arterial hypertension, is not recommended. (See section 4.5).

Fusidic acid: Co-administration of Lopinavir/ Ritonavir Oral granules with fusidic acid in osteo-articular infections is not recommended (see section 4.5).

Salmeterol: Co-administration of Lopinavir/ Ritonavir Oral granules with salmeterol is not recommended (see section 4.5).

Rivaroxaban: Co-administration of Lopinavir/ Ritonavir Oral granules with rivaroxaban is not recommended (see section4.5).

Vorapaxar: Co-administration of Lopinavir/ Ritonavir Oral granules with vorapaxar is not recommended. (See section4.5).

Riociguat: Co-administration of Lopinavir/ Ritonavir Oral granules with riociguat is not recommended. (See section 4.5).

Transmission
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/ Ritonavir Oral granules may still develop infections or other illnesses associated with HIVdisease and AIDS.
Excipients
Lopinavir/ Ritonavir Oral granules contains mannitol, which may have a mild laxative effect.
It is important to consider the contribution of ingredients from all the medicines that the patient is taking.

5. Interaction with other medicinal products and other forms of interaction
Lopinavir/ Ritonavir Oral granules contains lopinavir and ritonavir, both of which inhibit the P450 isoform CYP3A *in vitro*. Co-administration of Lopinavir/ Ritonavir Oral granules and medicinal products primarily metabolised by CYP3A may increase plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse reactions (see section 4.3). Lopinavir/ Ritonavir Oral granules does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations (see section 4.3).

Lopinavir/ritonavir has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some medicinal products metabolised by cytochrome P450 (including CYP2C9 and CYP2C19) enzymes and by glucuronidation. This may lower plasma concentrations and potentially decrease 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 not stated otherwise, were performed using lopinavir/ritonavir capsules (Kaletra®) at the dose of 400/100 mg twice daily.
Known and theoretical interactions with selected antiretroviral and non-antiretroviral medicinal products arelisted in the table below.

Interaction table
Interactions between Lopinavir/ Ritonavir Oral granules 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 oflopinavir/ritonavir (i.e. 400/100 mg twice daily).

Co-administered drug by therapeutic area	**Effects on drug levels** **Geometric Mean Change (%) in AUC, C_{max}, C_{min}** **Mechanism of interaction**	**Clinical recommendation concerning co-administration with Lopinavir/ Ritonavir Oral granules**

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 Lopinavir/ Ritonavir Oral granules .	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 Lopinavir/ Ritonavir Oral granules dosage should be increased to 500/125 mg twice daily when co-administered with efavirenz. Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules dosage should be increased to 500/125 mg twice daily when co-administered with nevirapine. Lopinavir/ Ritonavir Oral granules 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 : AUC: ↔ Cmin: ↓ 20% Cmax: ↔	No dose adjustment necessary
Rilpivirine (Lopinavir/ritonavir tablet	Rilpivirine: AUC: ↑ 52% Cmin: ↑ 74% Cmax: ↑ 29%Lopinavir:	Concomitant use of Lopinavir/ Ritonavir Oral granules with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required.

400/100 mg BID)	AUC: ↔ Cmin: ↓ 11% Cmax: ↔ (inhibition of CYP3Aenzymes)	
HIV CCR5-antagonist		
Maraviroc	Maraviroc: AUC: ↑ 295% Cmax: ↑ 97% Due to CYP3A inhibition bylopinavir/ritonavir.	The dose of maraviroc should be decreased to 150 mg twice daily during co-administration with Lopinavir/ Ritonavir Oral granules in doses of 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 notrecommended.		
Fosamprenavir/ ritonavir (700/100 mg BID) (Lopinavir/ritonavir 400/100 mgBID) or Fosamprenavir (1400 mg BID) (Lopinavir/ritonavir 533/133 mgBID)	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 notrecommended. Lopinavir/ Ritonavir Oral granules must not be administered once daily in combination with amprenavir.

Indinavir, 600 mg BID	Indinavir: AUC: ↔ Cmin: ↑ 3.5-foldCmax: ↓ (relative to indinavir 800 mgTID alone) Lopinavir: ↔ (relative to historical comparison)	The appropriate doses for this combination, 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 notrecommended.
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 Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules .	Careful monitoring of adverse effects (notably respiratory depression but also sedation) is recommended when fentanyl is concomitantly administered with Lopinavir/ Ritonavir Oral granules .
Antiarrhythmics		
Digoxin	Digoxin: Plasma concentrations may be increased due to P- glycoprotein inhibition by Lopinavir/ Ritonavir Oral granules. The increased digoxin level may lessen over time as Pgp	Caution is warranted and therapeutic drug monitoring of digoxin concentrations, if available, is recommended in case of co-administration of Lopinavir/ Ritonavir Oral granules and digoxin. Particular caution

	induction develops.	should be used when prescribing Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules.	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 Lopinavir/ Ritonavir Oral granules .	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 Lopinavir/ Ritonavir Oral granules to patients with impaired hepatic or renal function.
Anticancer agents		
Afatinib (Ritonavir 200 mg twice daily)	Afatinib: AUC: ↑ C_{max}: ↑ 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 lopinavir/ ritonavir.	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 lopinavir/ ritonavir.	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 Lopinavir/ Ritonavir Oral granules .	Careful monitoring of the tolerance of these anticancer agents.
Ibrutinib	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir	Co-administration of ibrutinib and Kaletra may increase ibrutinib exposure which may increase the risk of toxicity including risk of tumor lysis syndrome. Co-administration of ibrutinib and Kaletra should be avoided. If the benefit is considered to outweigh the risk and Kaletra must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.
Venetoclax	Due to CYP3A inhibition bylopinavir/ritonavir.	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir, resulting in increased risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase (see section 4.3 and refer to the venetoclax SmPC). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the

		venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax SmPC for dosing instructions). Patients should beclosely monitored for signs related to venetoclax toxicities.
Anticoagulants		
Warfarin	Warfarin: Concentrations may beaffected when co-administered with Lopinavir/ Ritonavir Oral granules due to CYP2C9induction.	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 Lopinavir/ Ritonavir Oral granules may increase rivaroxaban exposure which may increase the risk of bleeding. The use of rivaroxaban is not recommended in patients receiving concomitant treatment with Lopinavir/ Ritonavir Oral granules (see section 4.4).
Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	The co-administration of vorapaxar with Kaletra is not recommended (see section 4.4 and refer to the vorapaxar SmPC).
Anticonvulsants		
Phenytoin	Phenytoin: Steady-state concentrations were moderately decreased due to CYP2C9 and CYP2C19 induction by Lopinavir/ Ritonavir Oral granules. Lopinavir: Concentrations are decreased due to CYP3A induction by phenytoin.	Caution should be exercised in administering phenytoin with Lopinavir/ Ritonavir Oral granules. Phenytoin levels should be monitored when co-administering with lopinavir/ ritonavir. When co-administered with phenytoin, an increase of Lopinavir/ Ritonavir Oral granules dosage may be envisaged. Dose adjustment has not been

		evaluated in clinical practice. Lopinavir/ Ritonavir Oral granules must not be administered once daily in combination with phenytoin.
Carbamazepine and Phenobarbital	Carbamazepine: Serum concentrations may beincreased due to CYP3A inhibition by Lopinavir/ Ritonavir Oral granules. Lopinavir: Concentrations may be decreased due to CYP3A induction by carbamazepine and phenobarbital	Caution should be exercised in administering carbamazepine or phenobarbital with Lopinavir/ Ritonavir Oral granules. Carbamazepine and phenobarbital levels should be monitored when co-administering with lopinavir/ ritonavir. When co-administered with carbamazepine or phenobarbital, an increase of Lopinavir/ Ritonavir Oral granules dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules and valproic acid are given concomitantly. In patients starting or stopping Lopinavir/ Ritonavir Oral granules while currently taking maintenance dose of lamotrigine: Lamotrigine dose may need to be increased if [HA697 trade name] is added, or decreased if Lopinavir/ Ritonavir Oral granules is discontinued; therefore plasma lamotrigine monitoring should be conducted, particularly before and during 2 weeks after starting or stopping [HA697 trade name], in order to see if lamotrigine dose adjustment is needed

		In patients currently taking Lopinavir/ Ritonavir Oral granules 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 [HA697 trade name].	High doses of ketoconazole anditraconazole (> 200 mg/day) arenot recommended.
Voriconazole	Voriconazole: Concentrations may be decreased.	Co-administration of voriconazole and low dose ritonavir (100 mg BID) as contained in Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules 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), especially in patients with renal or hepatic impairment (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 Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules 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): AUC:↑30% A more pronounced effect on	Due to the risk of QTc prolongation associated with DM-6705, 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 4.4

	DM-6705 exposure may be observed during prolonged coadministration with lopinavir/ritonavir	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 Lopinavir/ Ritonavir Oral granules 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 neutropeniaand 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 Lopinavir/ Ritonavir Oral granules.
Rifampicin	Lopinavir: Large decreases in lopinavir concentrations may be observed due to CYP3A induction by rifampicin.	Co-administration of Lopinavir/ Ritonavir Oral granules with rifampicin is not recommended as the decrease in lopinavir concentrations may in turn significantly decrease the lopinavir therapeutic effect A dose adjustment of Lopinavir and Ritonavir 400 mg/400 mg (i.e. Lopinavir and Ritonavir 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 Lopinavir and Ritonavir Tablets at 400 mg/400 mg twice daily may be administered with rifampicin under close safety and therapeutic drug monitoring. The Lopinavir/ Ritonavir Oral granules dose should be titrated upward only after rifampicin has been initiated (see section 4.4).
Antipsychotics		
Quetiapine	Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapien are expected to increase.	Concomitant administration of Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules	Lopinavir/ Ritonavir Oral granules must not be co-administered with oral midazolam (see section 4.3), whereas caution should be used with co-administration of Lopinavir/ Ritonavir Oral granules and parenteral midazolam. If Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules 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 [HA697 trade name].	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with [HA697 trade name].
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 Lopinavir/ Ritonavir Oral granules .
Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone	Fluticasone propionate, 50 µg 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. Consequently, concomitant administration of Lopinavir/ Ritonavir Oral granules 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 aglucocorticoid, 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 bylopinavir/ritonavir.	The use of avanafil with Lopinavir/ Ritonavir Oral granules is contraindicated (see section 4.3).
Tadalafil	Tadalafil: AUC: ↑ 2-fold Due to CYP3A inhibition bylopinavir/ritonavir.	<u>For the treatment of pulmonary arterial hypertension:</u> Co-administration of Lopinavir/ Ritonavir Oral granules with sildenafil is contraindicated (see section 4.3). Co-administration of Lopinavir/ Ritonavir Oral granules with tadalafil is not recommended. <u>For erectile dysfunction:</u> particular caution must be used when prescribing sildenafil or tadalafil in patients receiving Lopinavir/ Ritonavir Oral granules with increased monitoring for adverse events including hypotension, syncope, visual changes and prolonged erection(see section 4.4). When co-administered with Lopinavir/ Ritonavir Oral granules , sildenafil doses must not exceed 25 mg in 48 hours and tadalafil doses must not exceed 10 mg every 72 hours.
Sildenafil	Sildenafil: AUC: ↑ 11-fold Due to CYP3A inhibition bylopinavir/ritonavir.	
Vardenafil	Vardenafil: AUC: ↑ 49-fold Due to CYP3A inhibition by Lopinavir/ Ritonavir Oral granules .	The use of vardenafil with Lopinavir/ Ritonavir Oral granules is contraindicated (see section 4.3).
HCV Protease Inhibitors		
Boceprevir 800 mg three timesdaily	Boceprevir: AUC: ↓ 45% Cmax: ↓ 50% Cmin: ↓ 57% Lopinavir: AUC: ↓ 34% Cmax: ↓ 30% Cmin: ↓ 43%	It is not recommended to co-administer Lopinavir/ Ritonavir Oral granules and boceprevir.
Simeprevir 200 mg daily (ritonavir 100 mgBID)	Simeprevir: AUC: ↑ 7.2-fold Cmax: ↑ 4.7-fold Cmin: ↑ 14.4-fold	It is not recommended to co-administer Lopinavir/ Ritonavir Oral granules and simeprevir
Telaprevir 750 mg three times daily	Telaprevir: AUC: ↓ 54% Cmax: ↓ 53% Cmin: ↓ 52%	It is not recommended to co-administer Lopinavir/ Ritonavir Oral granules and telaprevir.

	Lopinavir: ↔	
HCV direct acting antivirals		
Ombitasvir/ paritaprevir/ritonavir + dasabuvir (25/150/100 mg QD + 400 mgBID) Lopinavir/ritonavir 400/100 mg BID	Ombitasvir: ↔ Paritaprevir: AUC: ↑ 2.17-fold C_{max}: ↑ 2.04-fold C_{trough}: ↑ 2.36-fold (inhibition of CYP3A/ effluxtransporters) Dasabuvir: ↔ Lopinavir: ↔	Co-administration is contraindicated. Lopinavir/ritonavir 800/200 mg QD was administered with ombitasvir/paritaprevir/ritonavir with or without dasabuvir. The effect on DAAs and lopinavir was similar to that observed when lopinavir/ritonavir 400/100 mg BID was administered (see section 4.3).
Ombitasvir/ paritaprevir/ritonavir (25/150/100 mg QD) Lopinavir/ritonavir 400/100 mg BID	Ombitasvir: ↔ Paritaprevir: AUC: ↑ 6.10-fold C_{max}: ↑ 4.76-fold C_{trough}: ↑ 12.33-fold (inhibition of CYP3A/efflux transporters) Lopinavir: ↔	
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 Lopinavir/ Ritonavir Oral granules 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, Lopinavir/ Ritonavir Oral granules 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 [HA697 trade name].	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 Lopinavir/ Ritonavir Oral granules .	Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these agents with Lopinavir/ Ritonavir Oral granules is contraindicated (see section 4.3).
Atorvastatin	Atorvastatin: AUC: ↑ 5.9-fold Cmax: ↑ 4.7-fold Due to CYP3A inhibition by Lopinavir/ Ritonavir Oral granules .	The combination of Lopinavir/ Ritonavir Oral granules 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 Lopinavir/ Ritonavir Oral granules 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

		Lopinavir/ Ritonavir Oral granules 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 bybosentan. Bosentan: AUC: ↑ 5-fold Cmax: ↑ 6-fold Initially, bosentan Cmin: ↑ byapproximately 48-fold. Due to CYP3A4 inhibition by lopinavir/ ritonavir.	Caution should be exercised in administering Lopinavir/ Ritonavir Oral granules with bosentan. When Lopinavir/ Ritonavir Oral granules is administered concomitantly with bosentan, the efficacy ofthe 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 lopinavir/ritonavir.	The co-administration 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 Lopinavir/ Ritonavir Oral granules and dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole.		

6. Fertility, pregnancy and breast-feeding

Pregnancy

Lopinavir/ritonavir has been evaluated in over 3000 women during pregnancy, including over 1000 duringthe first trimester.

In post-marketing surveillance through the Antiretroviral Pregnancy Registry, established since January 1989, an increased risk of birth defects exposures with lopinavir/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/

Ritonavir Oral granules should only be used in pregnancy if the benefit clearly outweighs the risk.

Breast-feeding
Studies in rats revealed that lopinavir is present in the milk. It is not known whether this medicinal product is present in human milk. It is recommended that HIV-infected mothers should not breast-feed, in order to avoid the transmission of HIV. Only under specific circumstances the benefits of breast-feeding might be considered to outweigh the risks. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising patients on this matter.

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

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. Nevertheless, the clinical status of the patient and adverse reactions of Lopinavir/ Ritonavir Oral granules should be borne in mind when considering the patients' ability to drive or operate machinery.

8. Undesirable effects
The most common adverse reaction associated with lopinavir therapy is diarrhoea, nausea and vomiting, usually at the start of treatment. Also, dyslipidaemia, including hypertriglyceridaemia and hypercholesterolaemia are common, and may require drug treatment or discontinuation of tablet.

Pancreatitis has been reported in patients receiving ritonavir-boosted lopinavir. Furthermore, rare increases in the PR interval have been reported during therapy with ritonavir-boosted lopinavir (see section 4.4).

The following adverse reactions of moderate to severe intensity with possible or probable relationship to lopinavir/ritonavir have been reported. 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 rare (1/10 000 to 1/1,000). Events shown with a frequency, not known" were identified during post-marketing surveillance.

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common Common	Upper respiratory-tract infection 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 Uncommon	Hypersensitivity including urticaria and angioedema Immune reconstitution inflammatory syndrome
Endocrine disorders	Uncommon	Hypogonadism
Metabolism and nutritiondisorders	Common Uncommon	Blood glucose disorders including diabetes mellitus, hypertriglyceridaemia, hypercholesterolemia, weight decreased, decreased appetite Weight increased, increased appetite

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
Psychiatric disorders	Common Uncommon	Anxiety Abnormal dreams, libido decreased
Nervous system disorders	Common Uncommon	Headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, insomnia 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 Uncommon	Hypertension Deep-vein thrombosis
Gastrointestinal disorders	Very common Common Uncommon	Diarrhoea, nausea Pancreatitis (see section 4.4: pancreatitis and lipids), vomiting, gastro-oesophageal reflux disease, gastroenteritis and colitis, abdominal pain (upper and lower), abdominal distension, dyspepsia, haemorrhoids,flatulence Gastrointestinal haemorrhage including gastrointestinal ulcer, duodenitis, gastritis and rectal haemorrhage, stomatitis and oral ulcers, faecal incontinence, constipation, dry mouth
Hepatobiliary disorders	Common Uncommon Not known	Hepatitis including AST, ALT and GGT increases Hepatic steatosis, hepatomegaly, cholangitis, hyperbilirubinemia Jaundice
Skin and subcutaneous tissue disorders	Common Uncommon Not known	Rash including maculopapular rash, dermatitis/ rash including eczema and seborrheic dermatitis, night sweats,pruritus Alopecia, capillaritis, vasculitis Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue	Common	Myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such as weakness and

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
disorders	Uncommon	spasms Rhabdomyolysis, osteonecrosis
Renal and urinary disorders	Uncommon	Creatinine clearance decreased, nephritis, haematuria
Reproductive system andbreast disorders	Common	Erectile dysfunction, menstrual disorders - amenorrhea, menorrhagia
General disorders and administration site conditions	Common	Fatigue including asthenia

Description of selected adverse reactions
Cushings' 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.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (seesection 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 toonset 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 populations
In children 2 years of age and older, the nature of the safety profile is similar to that seen in adults.

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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the nationalreporting system.

9. Overdose
To date, there is limited human experience of acute overdose with lopinavir/ritonavir.

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

Therapy
There is no specific antidote for overdose with Lopinavir/ Ritonavir Oral granules. Treatment of overdose with Lopinavir/ Ritonavir Oral granules is general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, unabsorbed active substance may be eliminated by emesis or gastric lavage. Activated charcoal may also be used to aid removal of unabsorbed active substance. Since lopinavir and ritonavir are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaco-therapeutic 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/ Ritonavir Oral granules. Lopinavir inhibits 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.

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. In the absence of human serum, the mean IC_{50} of lopinavir against five different HIV-1 laboratory strains was 19 nM. In the absence and presence of 50% human serum, the mean IC_{50} of lopinavir against HIV-1_{IIIB} in MT4 cells was 17 nM and 102 nM, respectively. In the absence of human serum, the mean IC_{50} of lopinavir was 6.5 nM against several HIV-1 clinical isolates. Lopinavir also has in vitro activity against HIV-2, with median IC_{50} values similar to those for HIV-1.

Antiviral activity according to genotypic/phenotypic resistance: De novo resistance in treatment-naïve patients with prior wild-type virus failing therapy with ritonavir-boosted lopinavir in combination with NRTI is rare, provided that the patient is regularly monitored for viral load (e.g. 2–4 times annually after attaining undetectable HIV-RNA). For instance, in the pivotal phase 3 trial of ritonavir-boosted lopinavir (Kaletra®), 0/51 patients failing therapy had emergent protease inhibitor resistance mutations. Lack of resistance to lopinavir was confirmed by phenotypic analysis. Also, the level of resistance to the backbone therapy has been lower in previously treatment-naïve patients failing on ritonavir-boosted lopinavir therapy, compared with regimens not including a ritonavir-boosted PI.

In patients who have previously failed protease inhibitor therapy, incremental resistance may occur upon virological failure. Mutations V82A, I54V and M46I have emerged most frequently. Mutations L33F, I50V,V32I and I47V/A have also occurred.

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 the 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 EC_{50} of lopinavir against isolates with 0–3, 4–5, 6–7 and 8–10 mutations at the above amino acids was 0.8, 2.7, 13.5 and 44- fold higher than the EC_{50} against wild-type HIV, respectively. In addition to the mutations described above, mutations V32I and I47A have been observed in rebound isolates with reduced lopinavir susceptibility form protease inhibitor-experienced patients receiving ritonavir-boosted lopinavir therapy.

In studies of PI-experienced, NNRTI-naïve patients receiving therapy including ritonavir-boosted lopinavir, efavirenz and NRTIs, plasma HIV-RNA < 400 copies was observed at 48 weeks 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. In another study with a dataset from several clinical trials and cohorts, the changes in drug susceptibility associated with a 20% and 80% loss of predicted wild-type drug effect for lopinavir were 9.7- and 56-fold, respectively.

Clinically relevant resistance to lopinavir requires accumulation of resistance mutations in the

HIV-protease. Several genotypic resistance algorithms have been proposed for the quantification of the degree of phenotypic resistance to lopinavir, and for predicting the clinical response to lopinavir in protease inhibitorpre-treated patients. One of these, the lopinavir-ATU score, includes mutations at the following codons of the protease: 10, 20, 24, 33, 36, 47, 48, 54, 82 and 84.

With increasing resistance to lopinavir, resistance to other protease inhibitors will also increase to a varying degree, depending on the pattern of resistance mutations. Viruses with clinically relevant resistance to lopinavir are often susceptible to darunavir or tipranavir (refer to the SmPCs of these darunavir or tipranavir- containing products for information on genotypic predictors of response).

Table 1 Clinical cut-off values for reduced activity of ritonavir-boosted lopinavir by baselinegenotype/phenotype

	Activity not affected	**Decreased activity**	**Resistance**
LPV-ATU score[1] (no of mutations)	0–2	3–5	≥ 6
Clinical cut off Phenotype (fold change)[2]	< 10	10–60	> 60

1: Codons 10, 20, 24, 33, 36, 47, 48, 54, 82 and 84
2: These are approximate values; see text above. Assay: Antivirogram; Virco.

Clinical efficacy: Ritonavir-boosted lopinavir has been extensively studied in treatment-naïve and treatment- experienced adults and children**.** In various studies in treatment-naïve adults, the combination of ritonavir- boosted lopinavir and 2 NRTIs have yielded response rates (i.e. plasma viral load > 400 or > 50 copies/ml) inthe ITT population in the range of 70–80% at 48 weeks. In treatment-experienced patients the response rate varies depending on the activity of the background regimen and the sensitivity of the virus to lopinavir (see above).

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 ritonavir-boosted lopinavir, respectively. The two regimens resulted in exposures on Day 3 that were approximately 1.5- and 3-fold higher than those 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 samestudy 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 after dosing. Maximum PR interval was 286 msec and no second- or third-degree heart blockwas observed (see section 4.4).

5.2.Pharmacokinetic properties
The absorption characteristics of Lopinavir/ Ritonavir Oral granules have been determined after administration of singledose granules in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	Arithmetic mean value (± standard deviation)	
	Lopinavir	**Ritonavir**
Maximum concentration (C_{max})	482 (± 328) ng/mL	31 (± 16) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	4.490 (± 3.584) ng·h/mL	0.275 (± 0.160) ng·h/mL
Time to attain maximum concentration (Tmax)	5.46 (± 1.53) hours	4.89 (± 0.54) hours

Lopinavir is almost completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of ritonavir-boosted lopinavir 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 Lopinavir/ Ritonavir Oral granules is due to lopinavir.

Absorption
Multiple dosing with 400/100 mg Kaletra® twice daily for 2 weeks and without meal restriction 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. 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.

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. Lopinavir has been detected in cerebrospinal fluid at concentrations exceeding the IC_{50} of wild-type virus and has been shown toreduce HIV-RNA in cerebrospinal fluid.

Biotransformation
In vitro experiments 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. At least 13 metabolites of lopinavir have been identified, two of which are active; however, these are present at very low levels. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and the induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline during multiple dosing, stabilising after 10 days to 2 weeks.

Elimination
After administering radio-labelled lopinavir with ritonavir, approximately 10% and 83% of an administered dose was accounted for 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 6–7 litre/hour.

Special populations
Paediatrics: There are limited pharmacokinetic data in children below 2 years of age.
Gender, race and age: Lopinavir/ritonavir pharmacokinetics have not been studied in the elderly. No age-,gender- or race-related effect has been observed in adult patients.

Renal insufficiency: Ritonavir-boosted lopinavir pharmacokinetics has not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearanceis 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, and is not expected to be of clinical relevance.

5.3. Preclinical safety data
Repeat-dose toxicity studies in rodent and dogs identified major target organs including the liver, kidney,thyroid, spleen and circulating red blood cells. Hepatic changes indicated cellular swelling with focal degeneration.
The exposures eliciting these changes were comparable to or below human clinical exposure. Mild renal tubular degeneration was confined to mice exposed to at least twice the

recommended human exposure; the kidney was unaffected in rats and dogs. Reduced serum thyroxine levels led to 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 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 15-fold the 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, embryofetotoxicity (pregnancy loss, decreased fetal viability, decreased fetal 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 non-genotoxic, 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
Copovidone, sorbitan monolaurate, colloidal silicon dioxide, ethyl cellulose, mannitol, acesulfame potassium, sodium stearyl fumarate and vanilla flavour.

6.2.Incompatibilities
Not applicable

6.3.Shelf life
24 months

6.4.Special precautions for storage
Do not store above 30°C. Store in the original container.

6.5.Nature and contents of container
Sachets, comprises of printed triple laminated roll with aluminium foil, soft, dull side PET and bright sidelaminated to PE film. 1,000 mg granules per sachet.
Pack size: 120 sachets per carton

6.6.Special precautions for disposal and other handling

Lopinavir/ Ritonavir Oral granules must be taken with a meal twice daily. Lopinavir/ Ritonavir Oral granules should be sprinkled/mixed with soft food such as applesauce or porridge, or mixed with liquid such as water, as described below. Lopinavir/ Ritonavir Oral granules should not be chewed or crushed.

For infants and young children older than 6 months of age who are able to take soft foods:

1. Determine the number of sachets needed to prepare a dose.
2. Prior to mixing, tap the sachet(s) to move all the granules to the bottom of the sachet(s).
3. Completely tear or cut off the top of the sachet(s) and make sure the sachet(s) are fully open.
4. Mixing with soft food such as applesauce or porridge: Using a spoon, mix the entire contents of the Lopinavir / Ritonavir Oral granules 40 mg / 10 mg sachet(s) with soft food (approximately 1teaspoon of soft food for 1 sachet; 2 teaspoons for 2 sachets, etc.) in a small cup or bowl. Make sure no granules/powder are left inside the sachet(s). Give or take all of the mixture. If any granules are left in the small cup/bowl or spoon, add more soft food to the granules and mix. Then give or take the mixture along with adequate drinking water, to ensure that no granules areleft behind in the mouth.
5. Mixing with liquid such as drinking water: Mix the entire contents of the Lopinavir / RitonavirOral granules 40 mg / 10 mg sachet(s) with approximately 5 - 15 ml of drinking water (1 teaspoon of water for 2 sachets; 2 teaspoons of water for 3 to 8 sachets; 3 teaspoons or 1 tablespoon for 10 sachets). Make sure no granules/powder are left inside the sachet(s). Give or take all of the mixture. If any granules are left in the spoon, add more liquid (water) and mix. Then give or take the mixture.
6. Administer the drug/food mixture within 2 hours of preparation. If not administered within 2hours of preparation, throw away the mixture and prepare a new dose.
7. No mixture of the granules and food is to be stored for later use.
8. Repeat above steps for next dose.

For infants not yet taking solid food, i.e. less than 6 months of age:

1. Determine the number of sachets needed to prepare a dose.
2. Prior to mixing, tap the sachet(s) to move all the granules to the bottom of the sachet(s).
3. Completely tear or cut off the top of the sachet(s) and make sure the sachet(s) are fully open.
4. Granules can be added to a small volume of expressed breast milk or formula in a spoon andgiven to the infant or put directly on the infants' tongue before breastfeeding.
5. Administer the entire dose of granules to the infant immediately.
6. It is important to make sure the infant has taken the entire dose of granules by limiting the breastmilk (or formula) used to an amount the infant is able to easily consume in few swallows (e.g. two or three teaspoons), which may be followed by additional breast milk (or formula) to ensurethe full dose is ingested.
7. Repeat above steps for next dose.

7. SUPPLIER

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills Hyderabad-500096
Telangana, India.

Manufactured by:

Mylan Laboratories Limited,
Plot No. 11, 12 & 13,
Indore Special Economic Zone,
Pharma Zone, Phase-II, Sector-III,
Pithampur – 454775, Dist – Dhar,
Madhya Pradesh, India.

8. MARKETING AUTHORISATION NUMBER(S)

TAN 22 HM 0028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/01/2022

10.DATE OF REVISION OF THE TEXT