ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets
Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets

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

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets

Approx 15.0 mm x 8.0 mm, white, film coated, ovaloid, biconvex beveled edge tablet debossed with 'MLR4' on one side of the tablet and plain on the other side.

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets

Approx 18.8 mm x 10.0 mm, white, film coated, ovaloid, biconvex beveled edge tablet debossed with 'MLR3' on one side of the tablet and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Posology

Adults and adolescents
The standard recommended dosage of lopinavir/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/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 diarrhoea (see section 4.8) compared to the recommended standard twice daily dosing.

Paediatric population (2 years of age and above)
The adult dose of lopinavir/ritonavir 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 m^2. For children weighing less than 40 kg or with a BSA between 0.5 and 1.4 m^2 and able to swallow tablets, please refer to the dosing guideline tables below. Based on the current data available, lopinavir/ritonavir should not be administered once daily in paediatric patients (see section 5.1).

Before prescribing lopinavir/ritonavir 100/25 mg tablets, infants and young children should be assessed for the ability to swallow intact tablets. For infants and young children unable to swallow tablets, more suitable formulations containing lopinavir/ritonavir should be checked for their availability.

The following table contains dosing guidelines for lopinavir/ritonavir 100/25 mg tablets based on body weight and BSA.

Paediatric dosing guidelines without concomitant efavirenz or nevirapine*		
Weight (kg)	Body Surface Area (m^2)	Recommended number of 100/25 mg tablets twice-daily
15 to 25	≥ 0.5 to < 0.9	2 tablets (200/50 mg)
> 25 to 35	≥ 0.9 to < 1.4	3 tablets (300/75 mg)
> 35	≥ 1.4	4 tablets (400/100 mg)

* weight based dosing recommendations are based on limited data

If more convenient for patients, the lopinavir/ritonavir 200/50 mg tablets may also be considered alone or in combination with the lopinavir/ritonavir 100/25 mg tablet to achieve the recommended dose.

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

BSA (m^2) = $\sqrt{}$ (Height (cm) X Weight (kg) / 3600)

Children less than 2 years of age
The safety and efficacy of lopinavir/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/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 (m^2)	Recommended lopinavir/ritonavir dosing (mg) twice daily. The adequate dosing may be achieved with the two available strengths of lopinavir/ritonavir 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

* The 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/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/ritonavir tablets are administered orally and must be swallowed whole and not chewed, broken or crushed. Lopinavir/ritonavir tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Severe hepatic insufficiency.

Lopinavir/Ritonavir Viatris tablets contain lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Lopinavir/ritonavir 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		
$Alpha_1$-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 (see section 4.5).

Medicinal product class	Medicinal products within class	Rationale
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid. The concomitant administration with fusidic acid is contraindicated in dermatological infections (see section 4.5).
Anticancer	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase (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 (see section 4.5).
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 (see section 4.5).
	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 (see section 4.5).
GI motility agent	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent (see section 4.5).
Hepatitis C virus direct acting antivirals	Elbasvir/grazoprevir	Increased risk of alanine transaminase (ALT) elevations (see section 4.5).
	Ombitasvir/paritaprevir/ritonavir with or without dasabuvir	Increased plasma concentrations of paritaprevir; thereby, increasing the risk of alanine transaminase (ALT) elevations (see section 4.5).
Lipid-modifying agents 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).

Medicinal product class	Medicinal products within class	Rationale
Microsomal triglyceride transfer protein (MTTP) inhibitor	Lomitapide	Increased plasma concentrations of lomitapide (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/ritonavir has not been established in patients with significant underlying liver disorders. Lopinavir/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/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/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 and autoimmune hepatitis) 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/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

Lopinavir/Ritonavir Viatris tablets contain lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Lopinavir/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/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/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/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/ritonavir. Co-administration of lopinavir/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/ritonavir is contraindicated (see section 4.3).

Particular caution must be used when prescribing lopinavir/ritonavir and medicinal products known to induce QT interval prolongation such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. Indeed, lopinavir/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 lopinavir/ritonavir in preclinical studies; therefore, the potential cardiac effects of lopinavir/ritonavir cannot be currently ruled out (see sections 4.8 and 5.3).

Co-administration of lopinavir/ritonavir with rifampicin is not recommended. Rifampicin in combination with lopinavir/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/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/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/ritonavir is not a cure for HIV infection or AIDS. People taking lopinavir/ritonavir may still develop infections or other illnesses associated with HIV disease and AIDS.

Lopinavir/Ritonavir Viatris contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Lopinavir/Ritonavir Viatris tablets contain lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A *in vitro*. Co-administration of lopinavir/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/ritonavir 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 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/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. This list is not intended to be inclusive or comprehensive. Individual SmPCs should be consulted.

Interaction table

Interactions between lopinavir/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, C_{max}, C_{min} Mechanism of interaction**	**Clinical recommendation concerning co-administration with Lopinavir/Ritonavir Viatris**
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.	The clinical significance of reduced abacavir and zidovudine concentrations is unknown.
Tenofovir disoproxil fumarate (DF), 300 mg QD (equivalent to 245 mg tenofovir disoproxil)	Tenofovir: AUC: ↑ 32% C_{max}: ↔ C_{min}: ↑ 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% C_{max}: ↓ 13% C_{min}: ↓ 42%	The Lopinavir/Ritonavir Viatris tablets dosage should be increased to 500/125 mg twice daily when co-administered with efavirenz. Lopinavir/Ritonavir Viatris 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% C_{max}: ↓ 19% C_{min}: ↓ 51%	The Lopinavir/Ritonavir Viatris tablets dosage should be increased to 500/125 mg twice daily when co-administered with nevirapine. Lopinavir/Ritonavir Viatris must not be administered once daily in combination with nevirapine.
Etravirine (Lopinavir/ritonavir tablet 400/100 mg BID)	Etravirine: AUC: ↓ 35% C_{min}: ↓ 45% C_{max}: ↓ 30% Lopinavir: AUC: ↔ C_{min}: ↓ 20% C_{max}: ↔	No dose adjustment necessary

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 Viatris**
Rilpivirine (Lopinavir/ritonavir capsule 400/100 mg BID)	Rilpivirine: AUC: ↑ 52% C_{min}: ↑ 74% C_{max}: ↑ 29% Lopinavir: AUC: ↔ C_{min}: ↓ 11% C_{max}: ↔ (inhibition of CYP3A enzymes)	Concomitant use of Lopinavir/Ritonavir Viatris with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required.
HIV CCR5 – antagonist		
Maraviroc	Maraviroc: AUC: ↑ 295% C_{max}: ↑ 97% Due to CYP3A inhibition by lopinavir/ritonavir.	The dose of maraviroc should be decreased to 150 mg twice daily during co-administration with Lopinavir/Ritonavir Viatris 400/100 mg twice daily.
Integrase inhibitor		
Raltegravir	Raltegravir: AUC: ↔ C_{max}: ↔ C_{12} : ↓ 30% Lopinavir: ↔	No dose adjustment necessary

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 Viatris**
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. Lopinavir/Ritonavir Viatris must not be administered once daily in combination with amprenavir.
Indinavir, 600 mg BID	Indinavir: AUC: ↔ C_{min}: ↑ 3.5-fold C_{max}: ↓ (relative to indinavir 800 mg TID 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% C_{min}: ↓ 70% C_{max}: ↓ 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
Alpha$_1$ adrenoreceptor antagonist		
Alfuzosin	Alfuzosin: Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of alfuzosin are expected to increase.	Concomitant administration of Lopinavir/Ritonavir Viatris and alfuzosin is contra-indicated (see section 4.3) as alfuzosin-related toxicity, including hypotension, may be increased.

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 Viatris**
Analgesics		
Fentanyl	Fentanyl: Increased risk of side-effects (respiratory depression, sedation) due to higher plasma concentrations because of CYP3A4 inhibition by lopinavir/ritonavir.	Careful monitoring of adverse effects (notably respiratory depression but also sedation) is recommended when fentanyl is concomitantly administered with Lopinavir/Ritonavir Viatris.
Antianginal		
Ranolazine	Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of ranolazine are expected to increase.	The concomitant administration of Lopinavir/Ritonavir Viatris and ranolazine is contraindicated (see section 4.3).
Antiarrhythmics		
Amiodarone, Dronedarone	Amiodarone, Dronedarone: Concentrations may be increased due to CYP3A4 inhibition by lopinavir/ritonavir.	Concomitant administration of Lopinavir/Ritonavir Viatris and amiodarone or dronedarone is 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 lopinavir/ritonavir. 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 Lopinavir/Ritonavir Viatris and digoxin. Particular caution should be used when prescribing Lopinavir/Ritonavir Viatris 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 Viatris 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.	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.	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 Viatris to patients with impaired hepatic or renal function.

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 Viatris**
Anticancer agents and kinase inhibitors		
Abemaciclib	Serum concentrations may be increased due to CYP3A inhibition by ritonavir.	Co administration of abemaciclib and Lopinavir/Ritonavir Viatris should be avoided. If this co administration is judged unavoidable, refer to the abemaciclib SmPC for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.
Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of lopinavir/ritonavir. Serum concentrations of apalutamide may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Decreased exposure of Lopinavir/Ritonavir Viatris may result in potential loss of virological response. In addition, co-administration of apalutamide and Lopinavir/Ritonavir Viatris may lead to serious adverse events including seizure due to higher apalutamide levels. Concomitant use of Lopinavir/Ritonavir Viatris with apalutamide is not recommended.
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 Lopinavir/Ritonavir Viatris. 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 Lopinavir/Ritonavir Viatris. 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.	Careful monitoring of the tolerance of these anticancer agents.

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 Viatris**
Encorafenib	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Co-administration of encorafenib with Lopinavir/Ritonavir Viatris may increase encorafenib exposure which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Co administration of encorafenib and Lopinavir/Ritonavir Viatris should be avoided. If the benefit is considered to outweigh the risk and Lopinavir/Ritonavir Viatris must be used, patients should be carefully monitored for safety.
Fostamatinib	Increase in fostamatinib metabolite R406 exposure	Co-administration of fostamatinib with Lopinavir/Ritonavir Viatris may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension, or diarrhoea. Refer to the fostamatinib SmPC for dose reduction recommendations if such events occur.
Ibrutinib	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Co-administration of ibrutinib and Lopinavir/Ritonavir Viatris may increase ibrutinib exposure which may increase the risk of toxicity including risk of tumor lysis syndrome. Co administration of ibrutinib and Lopinavir/Ritonavir Viatris should be avoided. If the benefit is considered to outweigh the risk and Lopinavir/Ritonavir Viatris must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.
Neratinib	Serum concentrations may be increased due to CYP3A inhibition by ritonavir.	Concomitant use of neratinib with Lopinavir/Ritonavir Viatris is contraindicated due to serious and/or life threatening potential reactions including hepatotoxicity (see section 4.3).

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 Viatris**
Venetoclax	Due to CYP3A inhibition by lopinavir/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 be closely monitored for signs related to venetoclax toxicities.
Anticoagulants		
Warfarin	Warfarin: Concentrations may be affected when co-administered with lopinavir/ritonavir due to CYP2C9 induction.	It is recommended that INR (international normalised ratio) be monitored.
Rivaroxaban (Ritonavir 600 mg twice daily)	Rivaroxaban: AUC: ↑ 153% C_{max}: ↑ 55% Due to CYP3A and P-gp inhibition by lopinavir/ritonavir.	Co-administration of rivaroxaban and Lopinavir/Ritonavir Viatris 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 Viatris (see section 4.4).
Dabigatran etexilate, Edoxaban	Dabigatran etexilate, Edoxaban: Serum concentrations may be increased due to P-gp inhibition by lopinavir/ritonavir.	Clinical monitoring and/or dose reduction of the direct oral anticoagulants (DOAC) should be considered when a DOAC transported by P-gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co-administered with Lopinavir/Ritonavir Viatris.
Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir	The coadministration of vorapaxar with Lopinavir/Ritonavir Viatris is not recommended (see section 4.4 and refer to the vorapaxar SmPC).
Anticonvulsants		

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 Viatris**
Phenytoin	Phenytoin: Steady-state concentrations was moderately decreased due to CYP2C9 and CYP2C19 induction by lopinavir/ritonavir. Lopinavir: Concentrations are decreased due to CYP3A induction by phenytoin.	Caution should be exercised in administering phenytoin with Lopinavir/Ritonavir Viatris. Phenytoin levels should be monitored when co-administering with Lopinavir/Ritonavir Viatris. When co-administered with phenytoin, an increase of Lopinavir/Ritonavir Viatris dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. Lopinavir/Ritonavir Viatris must not be administered once daily in combination with phenytoin.
Carbamazepine and Phenobarbital	Carbamazepine: Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir. 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 Viatris. Carbamazepine and phenobarbital levels should be monitored when co-administering with Lopinavir/Ritonavir Viatris. When co-administered with carbamazepine or phenobarbital, an increase of Lopinavir/Ritonavir Viatris dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. Lopinavir/Ritonavir Viatris must not be administered once daily in combination with carbamazepine and phenobarbital.

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 Viatris**
Lamotrigine and Valproate	Lamotrigine: AUC: ↓ 50% C_{max}: ↓ 46% C_{min}: ↓ 56% Due to induction of lamotrigine glucuronidation Valproate: ↓	Patients should be monitored closely for a decreased VPA effect when Lopinavir/Ritonavir Viatris and valproic acid or valproate are given concomitantly. <u>In patients starting or stopping Lopinavir/Ritonavir Viatris while currently taking maintenance dose of lamotrigine:</u> lamotrigine dose may need to be increased if Lopinavir/Ritonavir Viatris is added, or decreased if Lopinavir/Ritonavir Viatris is discontinued; therefore plasma lamotrigine monitoring should be conducted, particularly before and during 2 weeks after starting or stopping Lopinavir/Ritonavir Viatris, in order to see if lamotrigine dose adjustment is needed. <u>In patients currently taking Lopinavir/Ritonavir Viatris and starting lamotrigine</u>: 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 Viatris 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 lopinavir/ritonavir.	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 Lopinavir/Ritonavir Viatris tablets should be avoided unless an assessment of the benefit/risk to patient justifies the use of voriconazole.
Anti-gout agents		

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 Viatris**
Colchicine single dose (Ritonavir 200 mg twice daily)	Colchicine: AUC: ↑ 3-fold C_{max}: ↑ 1.8-fold Due to P-gp and/or CYP3A4 inhibition by ritonavir.	Concomitant administration of Lopinavir/Ritonavir Viatris 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 Lopinavir/Ritonavir Viatris is required. Refer to colchicine prescribing information.
Antihistamines		
Astemizole Terfenadine	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Concomitant administration of Lopinavir/Ritonavir Viatris and astemizole and terfenadine is contraindicated as it may increase the risk of serious arrhythmias from these agents (see section 4.3).

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 Viatris**
Anti-infectives		
Fusidic acid	Fusidic acid: Concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Concomitant administration of Lopinavir/Ritonavir Viatris 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% C_{max}: ↔ 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 Viatris should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with Lopinavir/Ritonavir Viatris 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 DM-6705 exposure may be observed during prolonged co-administration with lopinavir/ritonavir.	Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with Lopinavir/Ritonavir Viatris is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid SmPC).

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 Viatris**
Rifabutin, 150 mg QD	Rifabutin (parent drug and active 25-O-desacetyl metabolite): AUC:↑ 5.7-fold C_{max}:↑ 3.5-fold	When given with Lopinavir/Ritonavir Viatris 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 Lopinavir/Ritonavir Viatris.
Rifampicin	Lopinavir: Large decreases in lopinavir concentrations may be observed due to CYP3A induction by rifampicin.	Co-administration of Lopinavir/Ritonavir Viatris 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/Ritonavir Viatris 400 mg/400 mg (i.e. Lopinavir/Ritonavir Viatris 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/Ritonavir Viatris at 400 mg/400 mg twice daily may be administered with rifampicin under close safety and therapeutic drug monitoring. The Lopinavir/Ritonavir Viatris dose should be titrated upward only after rifampicin has been initiated (see section 4.4).

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 Viatris**
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).
Pimozide	Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of pimozide are expected to increase.	Concomitant administration of Lopinavir/Ritonavir Viatris and pimozide is contraindicated as it may increase the risk of serious haematologic abnormalities or other serious adverse effects from this agent (see section 4.3)
Quetiapine	Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase.	Concomitant administration of Lopinavir/Ritonavir Viatris 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	Lopinavir/Ritonavir Viatris must not be co-administered with oral midazolam (see section 4.3), whereas caution should be used with co-administration of Lopinavir/Ritonavir Viatris and parenteral midazolam. If Lopinavir/Ritonavir Viatris 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.
Beta$_2$-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 Viatris 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 lopinavir/ritonavir.	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with Lopinavir/Ritonavir Viatris.

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 Viatris**
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 Viatris.
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 and triamcinolone. Consequently, concomitant administration of Lopinavir/Ritonavir Viatris 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.

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 Viatris**
Phosphodiesterase (PDE5) inhibitors		
Avanafil (ritonavir 600 mg BID)	Avanafil: AUC: ↑ 13-fold Due to CYP3A inhibition by lopinavir/ritonavir.	The use of avanafil with Lopinavir/Ritonavir Viatris is contraindicated (see section 4.3).
Tadalafil	Tadalafil: AUC: ↑ 2-fold Due to CYP3A4 inhibition by lopinavir/ritonavir.	<u>For the treatment of pulmonary arterial hypertension:</u> Co-administration of Lopinavir/Ritonavir Viatris with sildenafil is contraindicated (see section 4.3). Co-administration of Lopinavir/Ritonavir Viatris 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 Viatris with increased monitoring for adverse events including hypotension, syncope, visual changes and prolonged erection (see section 4.4). When co-administered with Lopinavir/Ritonavir Viatris, 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 by lopinavir/ritonavir.	
Vardenafil	Vardenafil: AUC: ↑ 49-fold Due to CYP3A inhibition by lopinavir/ritonavir.	The use of vardenafil with Lopinavir/Ritonavir Viatris is contraindicated (see section 4.3).
Ergot alkaloids		
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Concomitant administration of Lopinavir/Ritonavir Viatris and ergot alkaloids are contraindicated as it may lead to acute ergot toxicity, including vasospasm and ischaemia (see section 4.3).
GI motility agent		
Cisapride	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Concomitant administration of Lopinavir/Ritonavir Viatris and cisapride is contraindicated as it may increase the risk of serious arrhythmias from this agent (see section 4.3).

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 Viatris**
HCV direct acting antivirals		
Elbasvir/grazoprevir (50/200 mg QD)	Elbasvir: AUC: ↑ 2.71-fold C_{max}: ↑ 1.87-fold C_{24}: ↑ 3.58-fold Grazoprevir: AUC: ↑ 11.86-fold C_{max}: ↑ 6.31-fold C_{24}: ↑ 20.70-fold (combinations of mechanisms including CYP3A inhibition) Lopinavir: ↔	Concomitant administration of elbasvir/grazoprevir with Lopinavir/Ritonavir Viatris is contraindicated (see section 4.3).
Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-glycoprotein, BCRP and OATP1B inhibition by lopinavir/ritonavir.	Concomitant administration of glecaprevir/pibrentasvir and Lopinavir/Ritonavir Viatris is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
Ombitasvir/paritaprevir/ritonavir + dasabuvir (25/150/100 mg QD + 400 mg BID) 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/efflux transporters) 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: ↔	
Sofosbuvir/velpatasvir/voxilaprevir	Serum concentrations of sofosbuvir, velpatasvir and voxilaprevir may be increased due to P-glycoprotein, BCRP and OATP1B1/3 inhibition by lopinavir/ritonavir. However, only the increase in voxilaprevir exposure is considered clinically relevant.	It is not recommended to co administer Lopinavir/Ritonavir Viatris and sofosbuvir/velpatasvir/voxilaprevir.

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 Viatris**
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 Viatris 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 Viatris 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 lopinavir/ritonavir.	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.	Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these agents with Lopinavir/Ritonavir Viatris is contraindicated (see section 4.3).
Lipid-modifying agents		
Lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of lomitapide are expected to increase.	Concomitant use of Lopinavir/Ritonavir Viatris with lomitapide is contraindicated (see prescribing information for lomitapide) (see section 4.3).
Atorvastatin	Atorvastatin: AUC: ↑ 5.9-fold C_{max}: ↑ 4.7-fold Due to CYP3A inhibition by lopinavir/ritonavir.	The combination of Lopinavir/Ritonavir Viatris 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).

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 Viatris**
Rosuvastatin, 20 mg QD	Rosuvastatin: AUC: ↑ 2-fold C_{max}: ↑ 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 Viatris 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 Viatris 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 C_{max} ↓ ~50% This effect may be due to induction of bupropion metabolism.	If the co-administration of Lopinavir/Ritonavir Viatris 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.
Thyroid hormone replacement therapy		
Levothyroxine	Post marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine.	Thyroid stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending lopinavir/ritonavir treatment.

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 Viatris**
Vasodilating agents		
Bosentan	Lopinavir - ritonavir: Lopinavir/ritonavir plasma concentrations may decrease due to CYP3A4 induction by bosentan. Bosentan: AUC: ↑ 5-fold C_{max}: ↑ 6-fold Initially, bosentan C_{min}: ↑ by approximately 48-fold. Due to CYP3A4 inhibition by lopinavir/ritonavir.	Caution should be exercised in administering Lopinavir/Ritonavir Viatris with bosentan. When Lopinavir/Ritonavir Viatris 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 lopinavir/ritonavir	The co-administration of riociguat with Lopinavir/Ritonavir Viatris 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 Viatris and dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole.		

4.6 Fertility, 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/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.

Breast-feeding

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 women living with HIV do not breast-feed their babies 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 machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of lopinavir/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/ritonavir was used in combination with efavirenz or nevirapine.

The most common adverse reactions related to lopinavir/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/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/ritonavir, including those who developed hypertriglyceridaemia. Furthermore, rare increases in PR interval have been reported during lopinavir/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), rare (≥1/10,000 to <1/1000) and not known (cannot be estimated from the available data).

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

System organ class	Frequency	Adverse reaction
	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	Pancreatitis[1], 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	Jaundice, hepatic steatosis, hepatomegaly, cholangitis, hyperbilirubinemia
Skin and subcutaneous tissue disorders	Common	Rash including maculopapular rash, dermatitis/rash including eczema and seborrheic dermatitis, night sweats, pruritus
	Uncommon	Alopecia, capillaritis, vasculitis
	Rare	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
	Not known	Nephrolithiasis
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 and autoimmune hepatitis) 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 populations

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 national reporting system listed in Appendix V.

4.9 Overdose

To date, there is limited human experience of acute overdose with lopinavir/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/ritonavir. Treatment of overdose with lopinavir/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/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/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 ms from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 ms.

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 ms 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 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.

Resistance

In vitro selection of 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/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/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 IC_{50} 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 EC_{50} 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 EC_{50} 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 lopinavir/ritonavir therapy, and mutations I47A and L76V have been observed in rebound isolates with reduced lopinavir susceptibility from patients receiving lopinavir/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/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 lopinavir/ritonavir therapy, with respect to baseline viral genotype and phenotype, in 56 patients previous failing therapy with multiple protease inhibitors. The EC_{50} of lopinavir against the 56 baseline viral isolates ranged from 0.6 to 96-fold higher than the EC_{50} against wild type HIV. After 48 weeks of treatment with lopinavir/ritonavir, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA $\leq$ 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 lopinavir/ritonavir 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/ritonavir.

Cross-resistance

Activity of other protease inhibitors against isolates that developed incremental resistance to lopinavir after lopinavir/ritonavir 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/ritonavir in protease inhibitor-experienced patients. The median fold IC_{50} 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 IC_{50} from 3.7- to 8-fold in the baseline and rebound isolates, respectively. Isolates retained susceptibility to tipranavir with a median increase of IC_{50} 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/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/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/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/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/ml (range: 2.6 to 6.8 log_{10} copies/ml).

Table 1

Outcomes at Week 48: Study M98-863		
	Lopinavir/ritonavir (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/mm^3)	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/ritonavir 800/200 mg once daily plus tenofovir DF and emtricitabine versus lopinavir/ritonavir 400/100 mg twice daily plus tenofovir DF and emtricitabine in 664 antiretroviral treatment-naïve patients. Given the pharmacokinetic interaction between lopinavir/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/ritonavir. Patients were randomised in a 1:1 ratio to receive either lopinavir/ritonavir 800/200 mg once daily (n = 333) or lopinavir/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 (equivalent to 245 mg tenofovir disoproxil). 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/mm^3) and mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/ml (range: 1.7 to 7.0 $\log_{10}$ copies/ml).

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/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/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/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	
	Lopinavir/ritonavir (N=100)
HIV RNA < 400 copies/ml	61%
HIV RNA < 50 copies/ml	59%
Mean increase from baseline in CD4+ T-cell count (cells/mm^3)	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/mm^3 (range: 4 to 952 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/ml (range: 1.7 to 6.6 $\log_{10}$ copies/ml). 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/mm^3)	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/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 m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. 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 m^2 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/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ 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/mm^3)	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/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 EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of lopinavir/ritonavir is due to lopinavir.

Absorption

Multiple dosing with 400/100 mg lopinavir/ritonavir 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.

Effects of food on oral absorption

Administration of a single 400/100 mg dose of lopinavir/ritonavir tablets under fed conditions (high fat, 872 kcal, 56% from fat) compared to fasted state was associated with no significant changes in C_{max} and AUC_{inf}. Therefore, lopinavir/ritonavir tablets may be taken with or without food. Lopinavir/ritonavir tablets have also shown less pharmacokinetic variability under all meal conditions compared to lopinavir/ritonavir 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/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 ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg lopinavir/ritonavir 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 ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and faeces, respectively. 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/ritonavir have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Lopinavir/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/ritonavir once daily for 2 weeks without meal restriction (n=16) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 14.8 ± 3.5 µg/ml, occurring approximately 6 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 5.4 µg/ml. 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 C_{min}/C_{trough} values of approximately 50%.

Special populations

Paediatrics
There are limited pharmacokinetic data in children below 2 years of age. The pharmacokinetics of lopinavir/ritonavir oral solution 300/75 mg/m^2 twice daily and 230/57.5 mg/m^2 twice daily have been studied in a total of 53 paediatric patients, ranging in age from 6 months to 12 years. The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 μg•h/ml, 8.2 ± 2.9 μg/ml and 3.4 ± 2.1 μg/ml, respectively after lopinavir/ritonavir oral solution 230/57.5 mg/m^2 twice daily without nevirapine (n=12), and were 85.8 ± 36.9 μg•h/ml, 10.0 ± 3.3 μg/ml and 3.6 ± 3.5 μg/ml, respectively after 300/75 mg/m^2 twice daily with nevirapine (n=12). The 230/57.5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen without nevirapine.

Gender, race and age
Lopinavir/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****
AUC_{0-12} μg•hr/mL	68.7 (20.6)	61.3 (22.7)	94.3 (30.3)
C_{max}	7.9 (21.1)	7.5 (18.7)	9.8 (24.3)
$C_{predose}$ μg /mL	4.7 (25.2)	4.3 (39.0)	6.5 (40.4)
* n = 18 for C_{max} ** n = 16 for $C_{predose}$			

Renal insufficiency
Lopinavir/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

Sorbitan laurate
Silica, colloidal anhydrous
Copovidone
Sodium stearyl fumarate

Film-coating
Hypromellose
Titanium dioxide (E171)
Macrogol
Hydroxypropylcellulose
Talc
Silica, colloidal anhydrous
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

HDPE bottle: After first opening, use within 120 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets
OPA/Al/PVC-aluminium blister pack. Pack sizes available are:
- 60 (2 cartons of 30 or 2 cartons of 30 x1unit dose) film-coated tablets.

HDPE bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad and desiccant. Pack sizes available are:
- 1 bottle of 60 film-coated tablets.

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
OPA/Al/PVC-aluminium blister pack. Pack sizes available are:
- 120 (4 cartons of 30 or 4 cartons of 30 x1 unit dose) or 360 (12 cartons of 30) film-coated tablets.

HDPE bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad and desiccant. Pack sizes available are:
- 1 bottle of 120 film-coated tablets.
- Multipack containing 360 (3 bottles of 120) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Viatris LimitedDamastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1067/001
EU/1/15/1067/002
EU/1/15/1067/003
EU/1/15/1067/004
EU/1/15/1067/005
EU/1/15/1067/006
EU/1/15/1067/007
EU/1/15/1067/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 January 2016
Date of latest renewal: 16 November 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Mylan Hungary Kft
H-2900 Komárom, Mylan utca 1
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

120 (4 packs of 30) film-coated tablets
120x1 (4 packs of 30x1) film-coated tablets
360 (12 packs of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris LimitedDamastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1067/004
EU/1/15/1067/006
EU/1/15/1067/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lopinavir/Ritonavir Viatris 200 mg/50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
30x1 film-coated tablets

5. METHOD AND ROUTEOF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/15/1067/004 – 120 Film-coated tablets
EU/1/15/1067/006 – 120x1 Film-coated tablets
EU/1/15/1067/005 – 360 Film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
lopinavir/ritonavir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (BOTTLE)

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

120 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 120 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1067/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lopinavir/Ritonavir Viatris 200 mg/50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF BOTTLE MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 360 (3 bottles of 120) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 120 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1067/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lopinavir/Ritonavir Viatris 200 mg/50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF BOTTLE MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

120 film-coated tablets

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(s) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 120 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/15/1067/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(s)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

120 film-coated tablets

5. METHOD AND ROUTE(s) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 120 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/15/1067/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

60 (2 packs of 30) film-coated tablets
60x1 (2 packs of 30x1) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1067/001
EU/1/15/1067/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lopinavir/Ritonavir Viatris 100 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
30x1 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/15/1067/001 – 60 Film-coated tablets
EU/1/15/1067/002 – 60x1 Film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets
lopinavir/ritonavir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (BOTTLE)

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

60 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 120 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1067/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lopinavir/Ritonavir Viatris 100 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE (LABEL)

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets
lopinavir/ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

60 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 120 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1067/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets
lopinavir/ritonavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you or your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lopinavir/Ritonavir Viatris is and what it is used for

- Your doctor has prescribed lopinavir/ritonavir to help to control your Human Immunodeficiency Virus (HIV) infection. Lopinavir/ritonavir does this by slowing down the spread of the infection in your body.
- Lopinavir/Ritonavir Viatris is not a cure for HIV infection or AIDS
- Lopinavir/ritonavir is used by children 2 years of age or older, adolescents and adults who are infected with HIV, the virus which causes AIDS.
- Lopinavir/Ritonavir Viatris contains the active substances lopinavir and ritonavir. Lopinavir/ritonavir is an antiretroviral medicine. It belongs to a group of medicines called protease inhibitors.
- Lopinavir/ritonavir is prescribed for use in combination with other antiviral medicines. Your doctor will discuss with you and determine which medicines are best for you.

2. What you need to know before you or your child takes Lopinavir/Ritonavir Viatris

Do not take Lopinavir/Ritonavir Viatris if:
- you are allergic to lopinavir, ritonavir or any of the other ingredients of this medicine (listed in section 6);
- you have severe liver problems.

Do not take Lopinavir/Ritonavir Viatris with any of the following medicines:
- astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription);
- midazolam taken orally (taken by mouth), triazolam (used to relieve anxiety and/or trouble sleeping);
- pimozide (used to treat schizophrenia);
- quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder);
- lurasidone (used to treat depression);
- ranolazine (used to treat chronic chest pain [angina]);
- cisapride (used to relieve certain stomach problems);
- ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches);
- amiodarone, dronedarone (used to treat abnormal heart beat);
- lovastatin, simvastatin (used to lower blood cholesterol);

- lomitapide (used to lower blood cholesterol);
- alfuzosin (used in men to treat symptoms of an enlarged prostate (benign prostatic hyperplasia (BPH));
- fusidic acid (used to treat skin infections caused by *Staphylococcus* bacteria such as impetigo and infected dermatitis. Fusidic acid used to treat long-term infections of the bones and joints may be taken under doctor's supervision (see **Other medicines and Lopinavir/Ritonavir Viatris** section);
- colchicine (used to treat gout) if you have kidney and/or liver problems (see the section on **Other medicines and Lopinavir/Ritonavir Viatris**);
- elbasvir/grazoprevir (used to treat chronic hepatitis C virus [HCV]);
- ombitasvir/paritaprevir/ritonavir with or without dasabuvir (used to treat chronic hepatitis C virus [HCV]);
- neratinib (used to treat breast cancer);
- avanafil or vardenafil (used to treat erectile dysfunction);
- sildenafil used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery). Sildenafil used to treat erectile dysfunction may be taken under doctor's supervision (see **Other medicines and Lopinavir/ritonavir Viatris** section);
- products that contain St John's wort (*Hypericum perforatum*).

Read the list of medicines below under 'Other medicines and Lopinavir/Ritonavir Viatris' for information on certain other medicines which require special care.

If you are currently taking any of these medicines, ask your doctor about making necessary changes either in the treatment for your other condition(s) or in your antiretroviral treatment.

Warnings and precautions

Talk to your doctor or pharmacist before taking Lopinavir/Ritonavir Viatris.

Important information

- People taking lopinavir/ritonavir may still develop infections or other illnesses associated with HIV disease and AIDS. It is therefore important that you remain under the supervision of your doctor while taking lopinavir/ritonavir.

Tell your doctor if you or your child have/had

- **Haemophilia** type A and B as lopinavir/ritonavir might increase the risk of bleeding.
- **Diabetes** as increased blood sugars has been reported in patients receiving lopinavir/ritonavir.
- A history of **liver problems** as patients with a history of liver disease, including chronic hepatitis B or C are at increased risk of severe and potentially fatal liver side effects.

Tell your doctor if you or your child experience

- Nausea, vomiting, abdominal pain, difficulty breathing and severe weakness of the muscles in the legs and arms as these symptoms may indicate raised lactic acid levels.
- Thirst, frequent urination, blurred vision or weight loss as this may indicate raised sugar levels in the blood.
- Nausea, vomiting, abdominal pain as large increases in the amount of triglycerides (fats in the blood) have been considered a risk factor for pancreatitis (inflammation of the pancreas) and these symptoms may suggest this condition.
  In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
  In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness,

weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.
- **Joint stiffness, aches and pains** (especially of the hip, knee and shoulder) and difficulty in movement as some patients taking these medicines may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression (reduction in the activity of the immune system), higher body mass index, among others, may be some of the many risk factors for developing this disease.
- **Muscle pain,** tenderness or weakness, particularly in combination with these medicines. On rare occasions these muscle disorders have been serious.
- Symptoms of dizziness, lightheadedness, fainting or sensation of abnormal heartbeats. Lopinavir/ritonavir may cause changes in your heart rhythm and the electrical activity of your heart. These changes may be seen on an ECG (electrocardiogram).

Other medicines and Lopinavir/Ritonavir Viatris

Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take any other medicines.
- antibiotics (e.g. rifabutin, rifampicin, clarithromycin);
- anticancer medicines (e.g. abemaciclib, afatinib, apalutamide, ceritinib, encorafenib, ibrutinib, venetoclax, most tyrosine kinases inhibitors such as dasatinib and nilotinib, also vincristine and vinblastine);
- anticoagulants (e.g. dabigatran etexilate, edoxaban, rivaroxaban, vorapaxar and warfarin);
- antidepressants (e.g. trazodone, bupropion);
- anti-epilepsy medicines (e.g. carbamazepine, phenytoin, phenobarbital, lamotrigine and valproate);
- antifungals (e.g. ketoconazole, itraconazole, voriconazole);
- anti-gout medicines (e.g. colchicine). You must not take Lopinavir/Ritonavir Viatris with colchicine if you have kidney and/or liver problems (see also '**Do not take Lopinavir/Ritonavir Viatris**' above);
- anti tuberculosis medicine (bedaquiline, delamanid);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (e.g. glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir);
- erectile dysfunction medicines (e.g. sildenafil and tadalafil);
- fusidic acid used to treat long-term infections of the bones and joints (e.g. osteomyelitis);
- heart medicines including:
  - digoxin;
  - calcium channel antagonists (e.g. felodipine, nifedipine, nicardipine);
  - medicines used to correct heart rhythm (e.g. bepridil, systemic lidocaine, quinidine);
- HIV CCR5-antagonist (e.g. maraviroc);
- HIV-1 integrase inhibitor (e.g. raltegravir);
- medicines used to treat low blood platelet count (e.g. fostamatinib);
- levothyroxine (used to treat thyroid problems);
- medicines used to lower blood cholesterol (e.g. atorvastatin, lovastatin, rosuvastatin or simvastatin);
- medicines used to treat asthma and other lung-related problems such as chronic obstructive pulmonary disease (COPD) (e.g. salmeterol);
- medicines used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery) (e.g. bosentan, riociguat, sildenafil, tadalafil);
- medicines affecting the immune system (e.g. cyclosporin, sirolimus (rapamycin), tacrolimus);
- medicines used for smoking cessation (e.g. bupropion);
- pain-relieving medicines (e.g. fentanyl);
- morphine-like medicines (e.g. methadone);
- non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g. efavirenz, nevirapine);
- oral contraceptive or using a patch contraceptive to prevent pregnancy (see section below titled **Contraceptives**);
- protease inhibitors (e.g. fosamprenavir, indinavir, ritonavir, saquinavir, tipranavir);
- sedatives (e.g. midazolam administered by injection);
- steroids (e.g. budesonide, dexamethasone, fluticasone propionate, ethinyl oestradiol, triamcinolone).

Read the list of medicines above 'Do not take Lopinavir/Ritonavir Viatris with any of the following medicines' for information on medicines that you must not take with lopinavir/ritonavir.

Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take any other medicines, including medicines obtained without prescription.

Erectile dysfunction medicines (avanafil, vardenafil, sildenafil, tadalafil)
- **Do not take lopinavir/ritonavir** if you are currently taking avanafil or vardenafil.
- You must not take lopinavir/ritonavir with sildenafil used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery) (see also **Do not take Lopinavir/Ritonavir Viatris** section above).
- If you take sildenafil or tadalafil and lopinavir/ritonavir together, you may be at risk of side effects such as low blood pressure, passing out, visual changes and penile erection lasting more than 4 hours. If an erection lasts longer than 4 hours, you should get medical help **immediately** to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

Contraceptives

- If you are currently using an oral contraceptive or using a patch contraceptive to prevent pregnancy, you should use an additional or different type of contraception (e.g. condom) as lopinavir/ritonavir may reduce the effectiveness of oral and patch contraceptives.

Pregnancy and breast-feeding

- Tell your doctor **immediately** if you are planning to have a baby, you are pregnant, think you may be pregnant or if you are breast-feeding.
- If you are breast-feeding or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.
- Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.

Driving and using machines

Lopinavir/ritonavir has not specifically been tested for its possible effects on the ability to drive a car or operate machines. Do not drive a car or operate machinery if you experience any side effects (e.g. nausea) that impact your ability to do so safely. Instead, contact your doctor.

Lopinavir/Ritonavir Viatris contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Lopinavir/Ritonavir Viatris

It is important that Lopinavir/Ritonavir Viatris tablets are swallowed whole and not chewed, broken or crushed. Patients who have difficulty in swallowing the tablets, should should check for the availabity of more suitable formulations.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure how you should take your medicine.

How much Lopinavir/Ritonavir Viatris should be taken and when?

Use in adults

- The usual adult dose is 400 mg/100 mg twice a day i.e. every 12 hours, in combination with other anti-HIV medicines. Adult patients who have not previously taken other antiviral medicines can also take

lopinavir/ritonavir tablets once daily as an 800 mg/200 mg dose. Your doctor will advise on the number of tablets to be taken. Adult patients who have previously taken other antiviral medicines can take lopinavir/ritonavir tablets once daily as an 800 mg/200 mg dose if their doctor decides it is appropriate.
- Lopinavir/ritonavir must not be taken once daily with efavirenz, nevirapine, carbamazepine, phenobarbital and phenytoin.
- Lopinavir/ritonavir tablets can be taken with or without food.

Use in children

- For children, your doctor will decide the right dose (number of tablets) based on the child's height and weight.
- Lopinavir/ritonavir tablets can be taken with or without food.

Lopinavir/ritonavir is also supplied as 100 mg/25 mg film-coated tablets.

If you or your child take more Lopinavir/Ritonavir Viatris than you should

- If you realise you have taken more lopinavir/ritonavir than you were supposed to, contact your doctor right away.
- If you cannot contact your doctor, go to the hospital.

If you or your child forget to take Lopinavir/Ritonavir Viatris

If you are taking lopinavir/ritonavir twice a day

- If you notice you miss a dose within 6 hours of your normal dosing time, take your missed dose as soon as possible, and then continue with your normal dose at the regular time as prescribed by your doctor.

- If you notice you miss a dose by more than 6 hours after your normal dosing time, do not take the missed dose. Take the next dose as usual. Do not take a double dose to make up for a forgotten dose.

If you are taking lopinavir/ritonavir once a day

- If you notice you miss a dose within 12 hours of your normal dosing time, take your missed dose as soon as possible, and then continue with your normal dose at the regular time as prescribed by your doctor.

- If you notice you miss a dose by more than 12 hours after your normal dosing time, do not take the missed dose. Take the next dose as usual. Do not take a double dose to make up for a forgotten dose.

If you or your child stop taking Lopinavir/Ritonavir Viatris

- Do not stop or change the daily dose of lopinavir/ritonavir without first consulting with your doctor.
- Lopinavir/ritonavir should always be taken every day to help control your HIV infection, no matter how much better you feel.
- Taking lopinavir/ritonavir as recommended should give you the best chance of delaying the development of resistance to the product.
- If a side effect is preventing you from taking lopinavir/ritonavir as directed tell your doctor right away.
- Always keep enough lopinavir/ritonavir on hand so you don't run out. When you travel or need to stay in the hospital make sure you will have enough lopinavir/ritonavir to last until you can get a new supply.
- Continue to take this medicine until your doctor tells you otherwise.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, lopinavir/ritonavir can cause side effects, although not everybody gets them. It may be difficult to tell which side effects have been caused by lopinavir/ritonavir and which may occur due to other medicines you take at the same time or by the complications of the HIV infection.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

The following side effects have been reported by patients who took this medicine. You should tell your doctor promptly about these or any other symptoms. If the condition persists or worsens, seek medical attention.

Very common: may affect more than 1 in 10 people
- diarrhoea;
- nausea;
- upper respiratory tract infection.

Common: may affect up to 1 in 10 people
- inflammation of the pancreas;
- vomiting, enlarged abdomen, pain in the lower and upper stomach area, passing wind, indigestion, decreased appetite, reflux from your stomach to your oesophagus which may cause pain;
  - **Tell your doctor** if you experience nausea, vomiting or abdominal pain as these may be suggestive of pancreatitis (inflammation of the pancreas).
- swelling or inflammation of the stomach, intestines and colon;
- increased cholesterol levels in your blood, increased triglycerides (a form of fat) levels in your blood, high blood pressure;
- decreased ability of the body to handle sugar including diabetes mellitus, weight loss;
- low number of red blood cells, low number of white blood cells which are usually used to fight infection;
- rash, eczema, accumulation of scales of greasy skin;
- dizziness, anxiety, difficulty in sleeping;
- feeling tired, lack of strength and energy, headache including migraine;
- haemorrhoids;
- inflammation of the liver including increased liver enzymes;
- allergic reactions including hives and inflammation in the mouth;
- lower respiratory tract infection;
- enlargement of the lymph nodes;
- impotence, abnormally heavy or extended menstrual flow or a lack of menstruation;
- muscle disorders such as weakness and spasms, pain in the joints, muscles and back;
- damage to nerves of the peripheral nervous system;
- night sweats, itching, rash including raised bumps on the skin, infection of the skin, inflammation of skin or hair pores, accumulation of fluid in the cells or tissues.

Uncommon: may affect up to 1 in 100 people
- abnormal dreams;
- loss or changed sense of taste;
- hair loss;
- an abnormality in your electrocardiogram (ECG) called atrioventricular block;
- plaque building up inside your arteries which could lead to heart attack and stroke;

- inflammation of blood vessels and capillaries;
- inflammation of the bile duct;
- uncontrolled shaking of the body;
- constipation;
- deep vein inflammation related to a blood clot;
- dry mouth;
- inability to control your bowels;
- inflammation of the first section of the small intestine just after the stomach, wound or ulcer in the digestive tract, bleeding from the intestinal tract or rectum;
- red blood cells in the urine;
- yellowing of the skin or whites of eyes (jaundice);
- fatty deposits in the liver, enlarged liver;
- lack of functioning of the testes;
- a flare-up of symptoms related to an inactive infection in your body (immune reconstitution);
- increased appetite;
- abnormally high level of bilirubin (a pigment produced from the breakdown of red blood cells) in the blood;
- decreased sexual desire;
- inflammation of the kidney;
- bone death caused by poor blood supply to the area;
- mouth sores or ulcerations, inflammation of the stomach and intestine;
- kidney failure;
- breakdown of muscle fibres resulting in the release of muscle fibre contents (myoglobin) into the bloodstream;
- a sound in one ear or both ears, such as buzzing, ringing or whistling;
- tremor;
- abnormal closure of one of the valves (tricuspid valve in your heart);
- vertigo (spinning feeling);
- eye disorder, abnormal vision;
- weight gain.

Rare: may affect up to 1 in 1,000 people
- severe or life-threatening skin rashes and blisters (Stevens-Johnson syndrome and erythema multiforme).

Not known: frequency cannot be estimated from the available data
- kidney stones.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lopinavir/Ritonavir Viatris

Keep this medicine out of the sight and reach of children.

This medicinal product does not require any special storage conditions.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

For plastic containers, use within 120 days after first opening.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lopinavir/Ritonavir Viatris contains

- The active substances are lopinavir and ritonavir
- The other ingredients are sorbitan laurate, colloidal anhydrous silica, copovidone, sodium stearyl fumarate, hypromellose, titanium dioxide (E171), macrogol, hydroxypropylcellulose, talc, polysorbate 80.

What Lopinavir/Ritonavir Viatris looks like and contents of the pack

Lopinavir/Ritonavir Viatris 200 mg/50 mg film-coated tablets are white, film coated, ovaloid, biconvex beveled edge tablets debossed with 'MLR3' on one side of the tablet and plain on the other side.

They are available in blister multipacks of 120, 120x1 (4 cartons of 30 or 30x1) or 360 (12 cartons of 30) film-coated tablets and in plastic bottles (containing a desiccant, which should **not** be eaten) of 120 film-coated tablets and a multipack containing 360 (3 bottles of 120) film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

Manufacturer

Mylan Hungary Kft
H-2900 Komárom, Mylan utca 1
Hungary

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Viatris
Tél/Tel: + 32 (0)2 658 61 00

България
Майлан ЕООД
Тел: +359 2 44 55 400

Lietuva
Viatris UAB
Tel: +370 5 205 1288

Luxembourg/Luxemburg
Viatris
Tél/Tel: + 32 (0)2 658 61 00
(Belgique/Belgien)

Česká republika
Viatris CZ s.r.o.
Tel: +420 222 004 400

Danmark
Viatris ApS
Tlf: +45 28 11 69 32

Deutschland
Viatris Healthcare GmbH
Tel: +49 800 0700 800

Eesti
Viatris OÜ
Tel: + 372 6363 052

Ελλάδα
Viatris Hellas Ltd
Τηλ: +30 2100 100 002

España
Viatris Pharmaceuticals, S.L.
Tel: + 34 900 102 712

France
Viatris Santé
Tél: +33 4 37 25 75 00

Hrvatska
Viatris Hrvatska d.o.o.
Tel: +385 1 23 50 599

Ireland
Viatris Limited
Tel: +353 1 8711600

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Viatris Italia S.r.l.
Tel: + 39 (0) 2 612 46921

Κύπρος
CPO Pharmaceuticals Limited
Τηλ: +357 22863100

Latvija

Magyarország
Viatris Healthcare Kft.
Tel.: + 36 1 465 2100

Malta
V.J. Salomone Pharma Ltd
Tel: + 356 21 22 01 74

Nederland
Mylan BV
Tel: + 31 (0)20 426 3300

Norge
Viatris AS
Tlf: + 47 66 75 33 00

Österreich
Arcana Arzneimittel GmbH
Tel: +43 1 416 2418

Polska
Viatris Healthcare Sp. z o.o.
Tel: + 48 22 546 64 00

Portugal
Mylan, Lda.
Tel: + 351 214 127 200

România
BGP Products SRL
Tel: + 40 372 579 000

Slovenija
Viatris d.o.o.
Tel: + 386 1 23 63 180

Slovenská republika
Viatris Slovakia s.r.o.
Tel: +421 2 32 199 100

Suomi/Finland
Viatris Oy
Puh/Tel: + 358 20 720 9555

Sverige
Viatris AB
Tel: + 46 (0)8 630 19 00

Viatris SIA
Tel: +371 676 055 80

This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets
lopinavir/ritonavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you or your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lopinavir/Ritonavir Viatris is and what it is used for

- Your doctor has prescribed lopinavir/ritonavir to help to control your Human Immunodeficiency Virus (HIV) infection. Lopinavir/ritonavir does this by slowing down the spread of the infection in your body. Lopinavir/ritonavir Viatris is not a cure for HIV infection or AIDS
- Lopinavir/ritonavir is used by children 2 years of age or older, adolescents and adults who are infected with HIV, the virus which causes AIDS.
- Lopinavir/Ritonavir Viatris contains the active substances lopinavir and ritonavir. Lopinavir/ritonavir is an antiretroviral medicine. It belongs to a group of medicines called protease inhibitors.
- Lopinavir/ritonavir is prescribed for use in combination with other antiviral medicines. Your doctor will discuss with you and determine which medicines are best for you.

2. What you need to know before you or your child takes Lopinavir/Ritonavir Viatris

Do not take Lopinavir/Ritonavir Viatris if:
- you are allergic to lopinavir, ritonavir or any of the other ingredients of this medicine (listed in section 6);
- you have severe liver problems.

Do not take Lopinavir/Ritonavir Viatris with any of the following medicines:
- astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription);
- midazolam taken orally (taken by mouth), triazolam (used to relieve anxiety and/or trouble sleeping);
- pimozide (used to treat schizophrenia);
- quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder);
- lurasidone (used to treat depression);
- ranolazine (used to treat chronic chest pain [angina]);
- cisapride (used to relieve certain stomach problems);
- ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches);
- amiodarone, dronedarone (used to treat abnormal heart beat);
- lovastatin, simvastatin (used to lower blood cholesterol);
- lomitapide (used to lower blood cholesterol);

- alfuzosin (used in men to treat symptoms of an enlarged prostate (benign prostatic hyperplasia (BPH));
- fusidic acid (used to treat skin infections caused by *Staphylococcus* bacteria such as impetigo and infected dermatitis. Fusidic acid used to treat long-term infections of the bones and joints may be taken under doctor's supervision (see **Other medicines and Lopinavir/Ritonavir Viatris** section);
- colchicine (used to treat gout) if you have kidney and/or liver problems (see the section on **Other medicines and Lopinavir/Ritonavir**); elbasvir/grazoprevir (used to treat chronic hepatitis C virus [HCV]);
- ombitasvir/paritaprevir/ritonavir with or without dasabuvir (used to treat chronic hepatitis C virus [HCV]);
- neratinib (used to treat breast cancer);
- avanafil or vardenafil (used to treat erectile dysfunction);
- sildenafil used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery). Sildenafil used to treat erectile dysfunction may be taken under doctor's supervision (see **Other medicines and Lopinavir/Ritonavir Viatris** section);
- products that contain St John's wort (*Hypericum perforatum*).

Read the list of medicines below under 'Other medicines and Lopinavir/Ritonavir Viatris' for information on certain other medicines which require special care.

If you are currently taking any of these medicines, ask your doctor about making necessary changes either in the treatment for your other condition(s) or in your antiretroviral treatment.

Warnings and precautions

Talk to your doctor or pharmacist before taking Lopinavir/Ritonavir Viatris.

Important information

- People taking lopinavir/ritonavir may still develop infections or other illnesses associated with HIV disease and AIDS. It is therefore important that you remain under the supervision of your doctor while taking lopinavir/ritonavir.

Tell your doctor if you or your child have/had

- **Haemophilia** type A and B as lopinavir/ritonavir might increase the risk of bleeding.
- **Diabetes** as increased blood sugars has been reported in patients receiving lopinavir/ritonavir.
- A history of **liver problems** as patients with a history of liver disease, including chronic hepatitis B or C are at increased risk of severe and potentially fatal liver side effects.

Tell your doctor if you or your child experience

- Nausea, vomiting, abdominal pain, difficulty breathing and severe weakness of the muscles in the legs and arms as these symptoms may indicate raised lactic acid levels.
- Thirst, frequent urination, blurred vision or weight loss as this may indicate raised sugar levels in the blood.
- Nausea, vomiting, abdominal pain as large increases in the amount of triglycerides (fats in the blood) have been considered a risk factor for pancreatitis (inflammation of the pancreas) and these symptoms may suggest this condition.
  In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
  In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness,

weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.
- **Joint stiffness, aches and pains** (especially of the hip, knee and shoulder) and difficulty in movement as some patients taking these medicines may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression (reduction in the activity of the immune system), higher body mass index, among others, may be some of the many risk factors for developing this disease.
- **Muscle pain,** tenderness or weakness, particularly in combination with these medicines. On rare occasions these muscle disorders have been serious.
- Symptoms of dizziness, lightheadedness, fainting or sensation of abnormal heartbeats. Lopinavir/ritonavir may cause changes in your heart rhythm and the electrical activity of your heart. These changes may be seen on an ECG (electrocardiogram).

Other medicines and Lopinavir/Ritonavir Viatris

Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take any other medicines.
- antibiotics (e.g. rifabutin, rifampicin, clarithromycin);
- anticancer medicines (e.g. abemaciclib, afatinib, apalutamide, ceritinib, encorafenib, ibrutinib, venetoclax, most tyrosine kinases inhibitors such as dasatinib and nilotinib, also vincristine and vinblastine);
- anticoagulants (e.g. dabigatran etexilate, edoxaban, rivaroxaban, vorapaxar and warfarin);
- antidepressants (e.g. trazodone, bupropion);
- anti-epilepsy medicines (e.g. carbamazepine, phenytoin, phenobarbital, lamotrigine and valproate);
- antifungals (e.g. ketoconazole, itraconazole, voriconazole);
- anti-gout medicines (e.g. colchicine). You must not take Lopinavir/Ritonavir Viatris with colchicine if you have kidney/liver problems (see also '**Do no take Lopinavir/Ritonavir Viatris**' above);
- anti tuberculosis medicine (bedaquiline, delamanid);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) in adults (e.g. glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir);
- erectile dysfunction medicines (e.g. sildenafil and tadalafil);
- fusidic acid used to treat long-term infections of the bones and joints (e.g. osteomyelitis);
- heart medicines including:
  - digoxin;
  - calcium channel antagonists (e.g. felodipine, nifedipine, nicardipine);
  - medicines used to correct heart rhythm (e.g. bepridil, systemic lidocaine, quinidine);
- HIV CCR5-antagonist (e.g. maraviroc);
- HIV-1 integrase inhibitor (e.g. raltegravir);
- medicines used to treat low blood platelet count (e.g; fostamatinib);
- levothyroxine (used to treat thyroid problems);
- medicines used to lower blood cholesterol (e.g. atorvastatin, lovastatin, rosuvastatin or simvastatin);
- medicines used to treat asthma and other lung-related problems such as chronic obstructive pulmonary disease (COPD) (e.g. salmeterol);
- medicines used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery) (e.g. bosentan, riociguat, sildenafil, tadalafil);
- medicines affecting the immune system (e.g. cyclosporin, sirolimus (rapamycin), tacrolimus);
- medicines used for smoking cessation (e.g. bupropion);
- pain-relieving medicines (e.g. fentanyl);
- morphine-like medicines (e.g. methadone);
- non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g. efavirenz, nevirapine);
- oral contraceptive or using a patch contraceptive to prevent pregnancy (see section below titled **Contraceptives**);
- protease inhibitors (e.g. fosamprenavir, indinavir, ritonavir, saquinavir, tipranavir);
- sedatives (e.g. midazolam administered by injection);
- steroids (e.g. budesonide, dexamethasone, fluticasone propionate, ethinyl oestradiol, triamcinolone).

Read the list of medicines above 'Do not take Lopinavir/Ritonavir Viatris with any of the following medicines' for information on medicines that you must not take with lopinavir/ritonavir.

Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take any other medicines, including medicines obtained without prescription.

Erectile dysfunction medicines (avanafil, vardenafil, sildenafil, tadalafil)
- **Do not take lopinavir/ritonavir** if you are currently taking avanafil or vardenafil.
- You must not take lopinavir/ritonavir with sildenafil used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery) (see also **Do not take Lopinavir/Ritonavir Viatris** section above).
- If you take sildenafil or tadalafil and lopinavir/ritonavir together, you may be at risk of side effects such as low blood pressure, passing out, visual changes and penile erection lasting more than 4 hours. If an erection lasts longer than 4 hours, you should get medical help **immediately** to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

Contraceptives

- If you are currently using an oral contraceptive or using a patch contraceptive to prevent pregnancy, you should use an additional or different type of contraception (e.g. condom) as lopinavir/ritonavir may reduce the effectiveness of oral and patch contraceptives.

Pregnancy and breast-feeding

- Tell your doctor **immediately** if you are planning to have a baby, you are pregnant, think you may be pregnant or if you are breast-feeding.
- If you are breast-feeding or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.
- Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.

Driving and using machines

Lopinavir/ritonavir has not specifically been tested for its possible effects on the ability to drive a car or operate machines. Do not drive a car or operate machinery if you experience any side effects (e.g. nausea) that impact your ability to do so safely. Instead, contact your doctor.

Lopinavir/Ritonavir Viatris contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Lopinavir/Ritonavir Viatris

It is important that Lopinavir/Ritonavir Viatris tablets are swallowed whole and not chewed, broken or crushed. Patients who have difficulty in swallowing the tablets, should should check for the availabity of more suitable formulations.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure how you should take your medicine.

How much Lopinavir/Ritonavir Viatris should be taken and when?

Use in adults

- The usual adult dose is 400 mg/100 mg twice a day i.e. every 12 hours, in combination with other anti-HIV medicines. Adult patients who have not previously taken other antiviral medicines can also take lopinavir/ritonavir tablets once daily as an 800 mg/200 mg dose. Your doctor will advise on the number of tablets to be taken. Adult patients who have previously taken other antiviral medicines can take lopinavir/ritonavir tablets once daily as an 800 mg/200 mg dose if their doctor decides it is appropriate.
- Lopinavir/ritonavir must not be taken once daily with efavirenz, nevirapine, carbamazepine, phenobarbital and phenytoin.
- Lopinavir/ritonavir tablets can be taken with or without food.

Use in children of 2 years of age and above

- For children, your doctor will decide the right dose (number of tablets) based on the child's height and weight.
- Lopinavir/ritonavir tablets can be taken with or without food.

Lopinavir/ritonavir is also supplied as 200 mg/50 mg film-coated tablets. Other forms of this medicine may be more suitable for children; ask your doctor or pharmacist.

If you or your child take more Lopinavir/Ritonavir Viatris than you should

- If you realise you have taken more lopinavir/ritonavir than you were supposed to, contact your doctor right away.
- If you cannot contact your doctor, go to the hospital.

If you or your child forget to take Lopinavir/Ritonavir Viatris

If you are taking lopinavir/ritonavir twice a day

- If you notice you miss a dose within 6 hours of your normal dosing time, take your missed dose as soon as possible, and then continue with your normal dose at the regular time as prescribed by your doctor.

- If you notice you miss a dose by more than 6 hours after your normal dosing time, do not take the missed dose. Take the next dose as usual. Do not take a double dose to make up for a forgotten dose.

If you are taking lopinavir/ritonavir once a day

- If you notice you miss a dose within 12 hours of your normal dosing time, take your missed dose as soon as possible, and then continue with your normal dose at the regular time as prescribed by your doctor.

- If you notice you miss a dose by more than 12 hours after your normal dosing time, do not take the missed dose. Take the next dose as usual. Do not take a double dose to make up for a forgotten dose.

If you or your child stop taking Lopinavir/Ritonavir Viatris

- Do not stop or change the daily dose of lopinavir/ritonavir without first consulting with your doctor.
- Lopinavir/ritonavir should always be taken every day to help control your HIV infection, no matter how much better you feel.
- Taking lopinavir/ritonavir as recommended should give you the best chance of delaying the development of resistance to the product.
- If a side effect is preventing you from taking lopinavir/ritonavir as directed tell your doctor right away.

- Always keep enough lopinavir/ritonavir on hand so you don't run out. When you travel or need to stay in the hospital make sure you will have enough lopinavir/ritonavir to last until you can get a new supply.
- Continue to take this medicine until your doctor tells you otherwise.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, lopinavir/ritonavir can cause side effects, although not everybody gets them. It may be difficult to tell which side effects have been caused by lopinavir/ritonavir and which may occur due to other medicines you take at the same time or by the complications of the HIV infection.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

The following side effects have been reported by patients who took this medicine. You should tell your doctor promptly about these or any other symptoms. If the condition persists or worsens, seek medical attention.

Very common: may affect more than 1 in 10 people.
- diarrhoea;
- nausea;
- upper respiratory tract infection.

Common: may affect up to 1 in 10 people
- inflammation of the pancreas;
  - vomiting, enlarged abdomen, pain in the lower and upper stomach area, passing wind, indigestion, decreased appetite, reflux from your stomach to your oesophagus which may cause pain; **Tell your doctor** if you experience nausea, vomiting or abdominal pain as these may be suggestive of pancreatitis (inflammation of the pancreas).
- swelling or inflammation of the stomach, intestines and colon;
- increased cholesterol levels in your blood, increased triglycerides (a form of fat) levels in your blood, high blood pressure;
- decreased ability of the body to handle sugar including diabetes mellitus, weight loss;
- low number of red blood cells, low number of white blood cells which are usually used to fight infection;
- rash, eczema, accumulation of scales of greasy skin;
- dizziness, anxiety, difficulty in sleeping;
- feeling tired, lack of strength and energy, headache including migraine;
- haemorrhoids;
- inflammation of the liver including increased liver enzymes;
- allergic reactions including hives and inflammation in the mouth;
- lower respiratory tract infection;
- enlargement of the lymph nodes;
- impotence, abnormally heavy or extended menstrual flow or a lack of menstruation;
- muscle disorders such as weakness and spasms, pain in the joints, muscles and back;
- damage to nerves of the peripheral nervous system;
- night sweats, itching, rash including raised bumps on the skin, infection of the skin, inflammation of skin or hair pores, accumulation of fluid in the cells or tissues.

Uncommon: may affect up to 1 in 100 people
- abnormal dreams;
- loss or changed sense of taste;

- hair loss;
- an abnormality in your electrocardiogram (ECG) called atrioventricular block;
- plaque building up inside your arteries which could lead to heart attack and stroke;
- inflammation of blood vessels and capillaries;
- inflammation of the bile duct;
- uncontrolled shaking of the body;
- constipation;
- deep vein inflammation related to a blood clot;
- dry mouth;
- inability to control your bowels;
- inflammation of the first section of the small intestine just after the stomach, wound or ulcer in the digestive tract, bleeding from the intestinal tract or rectum;
- red blood cells in the urine;
- yellowing of the skin or whites of eyes (jaundice);
- fatty deposits in the liver, enlarged liver;
- lack of functioning of the testes;
- a flare-up of symptoms related to an inactive infection in your body (immune reconstitution);
- increased appetite;
- abnormally high level of bilirubin (a pigment produced from the breakdown of red blood cells) in the blood;
- decreased sexual desire;
- inflammation of the kidney;
- bone death caused by poor blood supply to the area;
- mouth sores or ulcerations, inflammation of the stomach and intestine;
- kidney failure;
- breakdown of muscle fibres resulting in the release of muscle fibre contents (myoglobin) into the bloodstream;
- a sound in one ear or both ears, such as buzzing, ringing or whistling;
- tremor;
- abnormal closure of one of the valves (tricuspid valve in your heart);
- vertigo (spinning feeling);
- eye disorder, abnormal vision;
- weight gain.

Rare: may affect up to 1 in 1,000 people
- severe or life-threatening skin rashes and blisters (Stevens-Johnson syndrome and erythema multiforme).

Not known: frequency cannot be estimated from the available data
- kidney stones.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lopinavir/Ritonavir Viatris

Keep this medicine out of the sight and reach of children.

This medicinal product does not require any special storage conditions.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

For plastic containers, use within 120 days after first opening.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lopinavir/Ritonavir Viatris contains

- The active substances are lopinavir and ritonavir
- The other ingredients are sorbitan laurate, colloidal anhydrous silica, copovidone, sodium stearyl fumarate, hypromellose, titanium dioxide (E171), macrogol, hydroxypropylcellulose, talc, polysorbate 80.

What Lopinavir/Ritonavir Viatris looks like and contents of the pack

Lopinavir/Ritonavir Viatris 100 mg/25 mg film-coated tablets are white, film coated, ovaloid, biconvex beveled edge tablets debossed with 'MLR4' on one side of the tablet and plain on the other side.

They are available in blister multipacks of 60 or 60x1 (2 cartons of 30 or 30x1) film-coated tablets and in plastic bottles (containing a desiccant, which should **not** be eaten) of 60 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

Manufacturer

Mylan Hungary Kft
H-2900 Komárom, Mylan utca 1
Hungary

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Viatris
Tél/Tel: + 32 (0)2 658 61 00

България
Майлан ЕООД
Тел: +359 2 44 55 400

Česká republika
Viatris CZ s.r.o.
Tel: +420 222 004 400

Danmark
Viatris ApS
Tlf: +45 28 11 69 32

Deutschland
Viatris Healthcare GmbH
Tel: +49 800 0700 800

Eesti
Viatris OÜ
Tel: + 372 6363 052

Ελλάδα
Viatris Hellas Ltd
Τηλ: +30 2100 100 002

España
Viatris Pharmaceuticals, S.L.
Tel: + 34 900 102 712

France
Viatris Santé
Tél: +33 4 37 25 75 00

Hrvatska
Viatris Hrvatska d.o.o.
Tel: +385 1 23 50 599

Ireland
Viatris Limited
Tel: +353 1 8711600

Ísland
Icepharma hf.
Sími: +354 540 8000

Lietuva
Viatris UAB
Tel: + 370 5 205 1288

Luxembourg/Luxemburg
Viatris
Tél/Tel: + 32 (0)2 658 61 00
(Belgique/Belgien)

Magyarország
Viatris Healthcare Kft.
Tel.: + 36 1 465 2100

Malta
V.J Salomone Pharma Ltd
Tel: + 356 21 22 01 74

Nederland
Mylan BV
Tel: +31 (0)20 426 3300

Norge
Viatris AS
Tlf: + 47 66 75 33 00

Österreich
Arcana Arzneimittel GmbH
Tel: +43 1 416 2418

Polska
Viatris Helathcare Sp. z o.o.
Tel: + 48 22 546 64 00

Portugal
Mylan, Lda.
Tel: + 351 214 127 200

România
BGP Products SRL
Tel: +40 372 579 000

Slovenija
Viatris d.o.o.
Tel: + 386 1 23 63 180

Slovenská republika
Viatris Slovakia s.r.o.
Tel: +421 2 32 199 100

Italia
Viatris Italia S.r.l.
Tel: + 39 (0) 2 612 46921

Κύπρος
CPO Pharmaceuticals Limited
Τηλ: +357 22863100

Latvija
Viatris SIA
Tel: + 371 676 055 80

Suomi/Finland
Viatris Oy
Puh/Tel: +358 20 720 9555

Sverige
Viatris AB
Tel: + 46 (0)8 630 19 00

This leaflet was last revised in (to be completed nationally).

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.