WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA697 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 40 mg lopinavir and 10 mg ritonavir.

Each sachet contains 583 mg of mannitol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Granules for oral suspension

A white to creamish granular powder filled in a sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA697 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in infants and children aged over 2 weeks.

The choice of [HA697 trade name] to treat protease inhibitor-experienced HIV-1 infected patients should be based on individual viral resistance testing and their treatment history (see sections 4.4 and 5.1).

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

[HA697 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

The recommended dose of [HA697 trade name] for children is as follows:

Child's weight	**Dose**
3 kg to less than 6 kg	2 sachets twice daily (lopinavir 80 mg/ritonavir 20 mg twice daily)
6 kg to less than 10 kg	3 sachets twice daily (lopinavir 120 mg/ritonavir 30 mg twice daily)
10 kg to less than 14 kg	4 sachets twice daily (lopinavir 160 mg/ritonavir 40 mg twice daily)
14 kg to less than 20 kg*	5 sachets twice daily (lopinavir 200 mg/ritonavir 50 mg twice daily)
20 kg to less than 25 kg*	6 sachets twice daily (lopinavir 240 mg/ritonavir 60 mg twice daily)

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

*tablet formulations supplying larger amounts of lopinavir/ritonavir should be preferred if available

The doses should be taken approximately 12 hours apart.

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

Patients weighing more than 25 kg should be treated with an alternative formulation supplying more of the active substances.

Infants weighing less than 3 kg

Data is lacking on the use of [HA697 trade name] in neonates weighing less than 3 kg. If no other formulation exists, one sachet twice daily could be considered for neonates older than 2 weeks who weigh 2 to 3 kg.

Missed dose

If a dose is missed, it should be taken as soon as it is remembered. However, if the next dose is due within 6 hours, the missed dose should be skipped, and the next dose should be taken at the usual time. Then, the treatment should be continued as before.

Hepatic impairment

In HIV-infected patients with mild to moderate hepatic impairment, an approximate 30 % increase in lopinavir exposure has been observed but is not expected to be of clinical relevance (see section 5.2). No data are available in patients with severe hepatic impairment. [HA697 trade name] must not be given to these patients (see section 4.3).

Renal impairment

No dose adjustment is necessary in patients with renal impairment.

Method of administration

[HA697 trade name] should be taken with food. After opening the sachets, the granules should be mixed with soft food such as applesauce or porridge, or a liquid such as clean drinking water or expressed breast milk before consumption. For detailed instructions see section 6.6.

4.3 Contraindications

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

[HA697 trade name] must not be administered to patients with severe hepatic impairment.

[HA697 trade name] must not be administered concurrently with agents with a narrow therapeutic window that are substrates of the isoenzyme CYP3A4, including alfuzosin, ranolazine, amiodarone, dronedarone, bepridil, quinidine, lurasidone, pimozide, quetiapine, astemizole, terfenadine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir (with or without dasabuvir), oral midazolam, triazolam, clorazepate, diazepam, flurazepam, ergot derivatives, fusidic acid, neratinib, venetoclax, colchicine, simvastatin and lovastatin, lomitapide, avanafil, sildenafil and vardenafil. Inhibition of CYP3A4 by ritonavir could increase plasma concentrations of these agents, potentially causing serious or life-threatening reactions (see also sections 4.4 and 4.5).

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

4.4 Special warnings and precautions for use

Patients with coexisting conditions

Hepatic impairment: [HA697 trade name] is contraindicated in patients with severe liver impairment. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased

risk for severe and potentially fatal hepatic adverse reactions. For concomitant antiviral therapy for hepatitis B or C, refer to the relevant product information for these medicinal products.

Patients with liver dysfunction including chronic hepatitis have increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

Laboratory tests should be conducted before starting treatment with lopinavir and ritonavir and 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. Lopinavir and ritonavir are highly protein bound, therefore it is unlikely that they will be significantly removed by haemodialyis or peritoneal dialysis

Haemophilia: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with protease inhibitors. A causal relationship is likely but a biological explanation has not been elucidated. Patients with haemophilia should therefore be warned of the possibility of increased bleeding.

Specific adverse reactions

Lipid elevations: Treatment with lopinavir and ritonavir has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol should be measured before starting [HA697 trade name] and periodically during therapy. Particular caution should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders should be managed as clinically appropriate.

Pancreatitis: Cases of pancreatitis have been reported in patients receiving lopinavir and ritonavir. Most of these patients have had a history of pancreatitis or concurrent therapy with other medicinal products associated with pancreatitis. Marked triglyceride elevation is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormal laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and [HA697 trade name] therapy should be suspended if pancreatitis is diagnosed (see section 4.8).

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

*Weight and metabolic parameters:*An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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

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

Osteonecrosis: Osteonecrosis has been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Its aetiology is considered to be multifactorial and includes corticosteroid use, alcohol consumption, severe immunosuppression, and higher body mass index.

So far, this disorder has been reported mainly in adults. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

PR interval prolongation: Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rarely, second- or third-degree atrioventricular block has been reported in patients taking lopinavir/ritonavir who have underlying structural heart disease and conduction abnormalities or who are taking drugs that prolong the PR interval (such as verapamil or atazanavir). [HA697 trade name] should be used with caution in such patients (see sections 4.8, 5.1 and 5.3).

Warnings on specific interactions with other medicinal products

[HA697 trade name] contains ritonavir, which is a very potent inhibitor of the P450 isoform CYP3A. [HA697 trade name] 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 for further information.

Hormonal contraceptives: In case of co-administration of [HA697 trade name] with contraceptives containing ethinylestradiol, irrespective of the formulation (e.g. oral or patch), additional barrier or non-hormonal methods of contraception must be used.

Excipients

[HA697 trade name] contains mannitol, which may have a mild laxative effect.

It is important to consider the contribution of ingredients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

[HA697 trade name] contains lopinavir and ritonavir, both of which inhibit the P450 isoform CYP3A *in vitro*. Co-administration of [HA697 trade name] and medicinal products primarily metabolised by CYP3A may increase plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse reactions (see section 4.3). [HA697 trade name] does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations (see section 4.3).

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

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

QT-interval prolonging agents: Particular caution must be used when prescribing [HA697 trade name] and medicinal products that prolong QT interval such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. [HA697 trade name] could increase concentrations of the coadministered medicinal products and this may increase their associated cardiac adverse events (see also section 4.3 and 4.5). Cardiac events have been reported with lopinavir/ritonavir in preclinical studies: therefore, potential cardiac effects of [HA697 trade name] cannot be currently ruled out (see sections 4.8 and 5.3).

Interaction table

Known and theoretical interactions between [HA697 trade name] and selected 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 [HA697 trade name]**
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 [HA697 trade name].	The clinical significance of reduced abacavir and zidovudine concentrations is unknown.
Tenofovir, 300 mg QD	Tenofovir: AUC: ↑ 32% Cmax : ↔ Cmin : ↑ 51% Lopinavir: ↔	No dose adjustment necessary. Higher tenofovir concentrations could potentiate tenofovir associated adverse events, including renal disorders.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz, 600 mg QD	Lopinavir: AUC: ↓ 20% Cmax : ↓ 13% Cmin : ↓ 42%	The [HA697 trade name] dosage should be increased to 500/125 mg twice daily when co-administered with efavirenz. [HA697 trade name] must not be administered once daily in combination with efavirenz.
Efavirenz 600 mg QD (Lopinavir/ritonavir 500/125 mg BID)	Lopinavir: ↔ (Relative to 400/100 mg BID administered alone)	
Nevirapine, 200 mg BID	Lopinavir: AUC: ↓ 27% Cmax : ↓ 19% Cmin : ↓ 51%	The [HA697 trade name] dosage should be increased to 500/125 mg twice daily when co-administered with nevirapine. [HA697 trade name] must not be administered once daily in combination with nevirapine.
Etravirine (Lopinavir/ritonavir tablet 400/100 mg BID)	Etravirine : AUC: ↓ 35% Cmin: ↓ 45% Cmax: ↓ 30% Lopinavir : AUC: ↔ Cmin: ↓ 20% Cmax: ↔	No dose adjustment necessary
Rilpivirine	Rilpivirine: AUC: ↑ 52% Cmin: ↑ 74% Cmax: ↑ 29% Lopinavir:	Concomitant use of [HA697 trade name] with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required.

(Lopinavir/ritonavir tablet 400/100 mg BID)	AUC: ↔ Cmin: ↓ 11% Cmax: ↔ (inhibition of CYP3A enzymes)	
HIV CCR5-antagonist		
Maraviroc	Maraviroc: AUC: ↑ 295% Cmax: ↑ 97% Due to CYP3A inhibition by lopinavir/ritonavir.	The dose of maraviroc should be decreased to 150 mg twice daily during co-administration with [HA697 trade name] in doses of 400/100 mg twice daily.
Integrase inhibitor		
Raltegravir	Raltegravir: AUC: ↔ Cmax: ↔ C12: ↓ 30% Lopinavir: ↔	No dose adjustment necessary
Co-administration with other HIV protease inhibitors (PIs) <u>According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.</u>		
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. [HA697 trade name] must not be administered once daily in combination with amprenavir.
Indinavir, 600 mg BID	Indinavir: AUC: ↔ Cmin: ↑ 3.5-fold Cmax: ↓ (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% Cmin: ↓ 70% Cmax: ↓ 47%	Concomitant administration of these medicinal products is not recommended.
Acid reducing agents		
Omeprazole (40 mg QD)	Omeprazole: ↔ Lopinavir: ↔	No dose adjustment necessary

Ranitidine (150 mg single dose)	Ranitidine: ↔	No dose adjustment necessary
Alpha1 adrenoreceptor antagonist:		
Alfuzosin	Alfuzosin: Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of alfuzosin are expected to increase.	Concomitant administration of [HA697 trade name] and alfuzosin is contra-indicated (see section 4.3) as alfuzosin-related toxicity, including hypotension, may be increased.
Analgesics		
Fentanyl	Fentanyl: Increased risk of side-effects (respiratory depression, sedation) due to higher plasma concentrations because of CYP3A4 inhibition by [HA697 trade name].	Careful monitoring of adverse effects (notably respiratory depression but also sedation) is recommended when fentanyl is concomitantly administered with [HA697 trade name].
Antiarrhythmics		
Digoxin	Digoxin: Plasma concentrations may be increased due to P-glycoprotein inhibition by [HA697 trade name]. 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 [HA697 trade name] and digoxin. Particular caution should be used when prescribing [HA697 trade name] 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 [HA697 trade name] 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 [HA697 trade name].	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 [HA697 trade name].	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 [HA697 trade name] to patients with impaired hepatic or renal function.
Anticancer agents		
Afatinib (Ritonavir 200 mg twice daily)	Afatinib: AUC: ↑ C_{max}: ↑	Caution should be exercised in administering afatinib with [HA697 trade name]. Refer to the afatinib SmPC for dosage

	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.	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 [HA697 trade name]. 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 [HA697 trade name].	Careful monitoring of the tolerance of these anticancer agents.
Fostamatinib	Increase in fostamatinib metabolite R406 exposure.	Co-administration of fostamatinib with [HA697 trade name] 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 [HA697 trade name] may increase ibrutinib exposure which may increase the risk of toxicity including risk of tumor lysis syndrome. Co-administration of ibrutinib and[HA697 trade name] should be avoided. If the benefit is considered to outweigh the risk and[HA697 trade name] must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.
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 [HA697 trade name] due to CYP2C9 induction.	It is recommended that INR (international normalised ratio) be monitored.
Rivaroxaban (Ritonavir 600 mg twice daily)	Rivaroxaban: AUC: ↑ 153% Cmax: ↑ 55% Due to CYP3A and P-gp inhibition by lopinavir/ritonavir.	Co-administration of rivaroxaban and [HA697 trade name] may increase rivaroxaban exposure which may increase the risk of bleeding. The use of rivaroxaban is not recommended in patients receiving concomitant treatment with [HA697 trade name] (see section 4.4).
Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	The co-administration of vorapaxar with [HA697 trade name] is not recommended (see section 4.4 and refer to the vorapaxar SmPC).
Anticonvulsants		
Phenytoin	Phenytoin: Steady-state concentrations was moderately decreased due to CYP2C9 and CYP2C19 induction by [HA697 trade name]. Lopinavir: Concentrations are decreased due to CYP3A induction by phenytoin.	Caution should be exercised in administering phenytoin with [HA697 trade name]. Phenytoin levels should be monitored when co-administering with lopinavir/ritonavir. When co-administered with phenytoin, an increase of [HA697 trade name] dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. [HA697 trade name] must not be administered once daily in combination with phenytoin.
Carbamazepine and Phenobarbital	Carbamazepine: Serum concentrations may be increased due to CYP3A inhibition by [HA697 trade name].	Caution should be exercised in administering carbamazepine or phenobarbital with [HA697 trade name]. Carbamazepine and phenobarbital levels should be monitored when

	Lopinavir: Concentrations may be decreased due to CYP3A induction by carbamazepine and phenobarbital	co-administering with lopinavir/ritonavir. When co-administered with carbamazepine or phenobarbital, an increase of [HA697 trade name] dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. [HA697 trade name] must not be administered once daily in combination with carbamazepine and phenobarbital.
Lamotrigine and Valproate	Lamotrigine: AUC: ↓ 50% Cmax: ↓ 46% Cmin: ↓ 56% Due to induction of lamotrigine glucuronidation Valproate: ↓	Patients should be monitored closely for a decreased VPA effect when [HA697 trade name] and valproic acid are given concomitantly. <u>In patients starting or stopping [HA697 trade name] while currently taking maintenance dose of lamotrigine:</u> Lamotrigine dose may need to be increased if [HA697 trade name] is added, or decreased if [HA697 trade name] is discontinued; therefore plasma lamotrigine monitoring should be conducted, particularly before and during 2 weeks after starting or stopping [HA697 trade name], in order to see if lamotrigine dose adjustment is needed. <u>In patients currently taking [HA697 trade name] 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 causes a similar increase in trazodone exposure. The combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals		
Ketoconazole and Itraconazole	Ketoconazole, Itraconazole: Serum concentrations may be increased due to CYP3A inhibition by [HA697 trade name].	High doses of ketoconazole 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 [HA697 trade name] should be avoided unless an assessment of the benefit/risk to patient justifies the use of voriconazole.
Anti-gout agents:		
Colchicine single dose (Ritonavir 200 mg twice daily)	Colchicine: AUC : ↑ 3-fold Cmax : ↑ 1.8-fold Due to P-gp and/or CYP3A4 inhibition by ritonavir.	Concomitant administration of [HA697 trade name] with colchicine in patients with renal and/or hepatic impairment is contraindicated due to a potential increase of colchicine-related serious and/or life-threatening reactions such as neuromuscular toxicity (including rhabdomyolysis), especially in patients with renal or hepatic impairment (see section 4.3). A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with [HA697 trade name] 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 [HA697 trade name] and astemizole and terfenadine is contraindicated as it may increase the risk of serious arrhythmias from these agents (see section 4.3).
Anti-infectives:		
Fusidic acid	Fusidic acid: Concentrations may be increased due to CYP3A inhibition by lopinavir/ritonavir.	Concomitant administration of [HA697 trade name] with fusidic acid is contra-indicated in dermatological indications due to the increased risk of adverse events related to fusidic acid, notably rhabdomyolysis (see section 4.3). When used for osteo-articular infections, where the co-administration is unavoidable, close clinical monitoring for muscular adverse events is strongly recommended (see section 4.4).
Antimycobacterials		
Bedaquiline (single dose) (Lopinavir/ritonavir 400/100 mg BID, multiple dose)	Bedaquiline: AUC: ↑ 22% Cmax: ↔ A more pronounced effect on bedaquiline plasma exposures may be observed during	Due to the risk of bedaquiline related adverse events, the combination of bedaquiline and lopinavir/ritonavir should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with lopinavir/ritonavir

	prolonged co-administration with lopinavir/ritonavir. CYP3A4 inhibition likely due to lopinavir/ritonavir	must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (refer also 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 coadministration with lopinavir/ritonavir	Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (refer also to the delamanid SmPC).
Rifabutin, 150 mg QD	Rifabutin (parent drug and active 25-O-desacetyl metabolite): AUC: ↑ 5.7-fold Cmax: ↑ 3.5-fold	When given with [HA697 trade name] 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 [HA697 trade name].
Rifampicin	Lopinavir: Large decreases in lopinavir concentrations may be observed due to CYP3A induction by rifampicin.	Co-administration of [HA697 trade name] with rifampicin is not recommended as the decrease in lopinavir concentrations may in turn significantly decrease the lopinavir therapeutic effect Administration of additional ritonavir (i.e. lopinavir and ritonavir 400/100 mg + ritonavir 300 mg) twice daily can compensate for CYP 3A4

		induction by rifampicin. However, such a dose adjustment might be associated with ALT/AST elevations and with increase in gastrointestinal disorders. Therefore, such a combination should be avoided unless strictly necessaryand only given with close safety and therapeutic drug monitoring. The ritonavir dose should be titrated upward only after rifampicin has been initiated.
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 [HA697 trade name] 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 quetiapien are expected to increase.	Concomitant administration of [HA697 trade name] 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 [HA697 trade name]	[HA697 trade name] must not be co-administered with oral midazolam (see section 4.3), whereas caution should be used with co-administration of [HA697 trade name] and parenteral midazolam. If [HA697 trade name] 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.
Alprazolam Diazepam Triazolam		[HA697 trade name] should not be used concomitantly with strongly sedative drugs metabolized by CYP3A, such as alprazolam, diazepam or triazolam, as this may result in excessive effects
Oxazepam		Oxazepam is not metabolised by CYP3A; however, due to induction of glucuronidation, an increased dose of oxazepam may be

		necessary when co-treating with [HA697 trade name].
Beta2-adrenoceptor agonist (long acting)		
Salmeterol	Salmeterol: Concentrations are expected to increase due to CYP3A inhibition by lopinavir/ritonavir.	The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Therefore, concomitant administration of [HA697 trade name] with salmeterol is not recommended (see section 4.4).
Calcium channel blockers		
Felodipine, Nifedipine, and Nicardipine	Felodipine, Nifedipine, Nicardipine: Concentrations may be increased due to CYP3A inhibition by [HA697 trade name].	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with [HA697 trade name].
Corticosteroids		
Dexamethasone	Lopinavir: Concentrations may be decreased due to CYP3A induction by dexamethasone.	Clinical monitoring of antiviral efficacy is recommended when these medicines are concomitantly administered with [HA697 trade name].
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 eg budesonide. Consequently, concomitant administration of [HA697 trade name] 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 (eg beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period.
Phosphodiesterase(PDE5) inhibitors		

Avanafil (ritonavir 600 mg BID)	Avanafil: AUC: ↑ 13-fold Due to CYP3A inhibition by lopinavir/ritonavir.	The use of avanafil with [HA697 trade name] is contraindicated (see section 4.3).
Tadalafil	Tadalafil: AUC: ↑ 2-fold Due to CYP3A inhibition by lopinavir/ritonavir.	<u>For the treatment of pulmonary arterial hypertension:</u> Co-administration of [HA697 trade name] with sildenafil is contraindicated (see section 4.3). Co-administration of [HA697 trade name] with tadalafil is not recommended. <u>For erectile dysfunction:</u> particular caution must be used when prescribing sildenafil or tadalafil in patients receiving [HA697 trade name] with increased monitoring for adverse events including hypotension, syncope, visual changes and prolonged erection (see section 4.4). When co-administered with [HA697 trade name], 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 [HA697 trade name].	The use of vardenafil with [HA697 trade name] is contraindicated (see section 4.3).
HCV Protease Inhibitors		
Boceprevir 800 mg three times daily	Boceprevir: AUC: ↓ 45% Cmax: ↓ 50% Cmin: ↓ 57% Lopinavir: AUC: ↓ 34% Cmax: ↓ 30% Cmin: ↓ 43%	It is not recommended to co-administer [HA697 trade name] and boceprevir.
Simeprevir 200 mg daily (ritonavir 100 mg BID)	Simeprevir: AUC: ↑ 7.2-fold Cmax: ↑ 4.7-fold Cmin: ↑ 14.4-fold	It is not recommended to co-administer [HA697 trade name] andsimeprevir
Telaprevir 750 mg three times daily	Telaprevir: AUC: ↓ 54% Cmax: ↓ 53% Cmin: ↓ 52% Lopinavir: ↔	It is not recommended to co-administer [HA697 trade name] and telaprevir.
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	Concomitant administration of elbasvir/grazoprevir with [HA697

	Grazoprevir: AUC: ↑ 11.86-fold C_{max}: ↑ 6.31-fold C_{24}: ↑ 20.70-fold (combinations of mechanisms including CYP3A inhibition) Lopinavir: ↔	trade name] 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 [HA697 trade name] 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 [HA697 trade name] and sofosbuvir/velpatasvir/ voxilaprevir.
HCV protease inhibitors		
Simeprevir 200 mg daily (ritonavir 100 mg BID)	Simeprevir: AUC: ↑ 7.2-fold Cmax: ↑ 4.7-fold	It is not recommended to co-administer [HA697 trade name] and simeprevir.

	Cmin: ↑ 14.4-fold	
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 [HA697 trade name] 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, [HA697 trade name] can be started safely 2 weeks after cessation of St. John's wort.
Immunosuppressants		
Cyclosporin, Sirolimus (rapamycin), and Tacrolimus	Cyclosporin, Sirolimus (rapamycin), Tacrolimus: Concentrations may be increased due to CYP3A inhibition by [HA697 trade name].	More frequent therapeutic concentration monitoring is recommended until plasma levels of these products have been stabilised.
Lipid lowering agents		
Lovastatin and Simvastatin	Lovastatin, Simvastatin: Markedly increased plasma concentrations due to CYP3A inhibition by [HA697 trade name].	Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these agents with [HA697 trade name] is contraindicated (see section 4.3).
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 [HA697 trade name] with lomitapide is contraindicated (see prescribing information for lomitapide) (see section 4.3).
Atorvastatin	Atorvastatin: AUC: ↑ 5.9-fold Cmax: ↑ 4.7-fold Due to CYP3A inhibition by [HA697 trade name].	The combination of [HA697 trade name] with atorvastatin is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring (see section 4.4).
Rosuvastatin, 20 mg QD	Rosuvastatin: AUC: ↑ 2-fold Cmax: ↑ 5-fold While rosuvastatin is poorly metabolised by CYP3A4, an increase of its plasma concentrations was observed.	Caution should be exercised and reduced doses should be considered when [HA697 trade name] is co-administered with rosuvastatin (see section 4.4).

	The mechanism of this interaction may result from inhibition of transport proteins.	
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.
Fentanyl Pethidine Propoxyphene		[HA697 trade name] should not be used concomitantly with strongly sedative drugs metabolized by CYP3A,such as fentanyl, pethidine or propoxyphene, as this may result in excessive effects.
Morphine		Morphine is not metabolised by CYP3A; however, due to induction of glucuronidation, an increased dose of morphine may be necessary when co-treating with [HA697 trade name]
Oral Contraceptives		
Ethinyl Oestradiol	Ethinyl Oestradiol: ↓	The decreased systemic exposure to the oestrogen component may not only reduce contraceptive efficacy but also alter the uterine bleeding profile. In case of co-administration of [HA697 trade name] with contraceptives containing ethinyl oestradiol (whatever the contraceptive formulation e.g. oral or patch), additional methods of contraception must be used.
Smoking cessation aids		
Bupropion	Buproprion and its active metabolite, hydroxybupropion: AUC and Cmax ↓ ~50% This effect may be due to induction of bupropion metabolism.	If the co-administration of lopinavir/ritonavir with bupropion is judged unavoidable, this should be done under close clinical monitoring for bupropion efficacy, without exceeding the recommended dosage, despite the observed induction.
Vasodilating agents:		
Bosentan	Lopinavir - ritonavir: Lopinavir/ritonavir plasma concentrations may decrease due to CYP3A4 induction by bosentan. Bosentan:	Caution should be exercised in administering [HA697 trade name] with bosentan. When [HA697 trade name] is administered concomitantly with bosentan, the efficacy of the HIV therapy should be monitored and

	AUC: ↑ 5-fold Cmax: ↑ 6-fold Initially, bosentan Cmin : ↑ by approximately 48-fold. Due to CYP3A4 inhibition by lopinavir/ritonavir.	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 [HA697 trade name] 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 [HA697 trade name] and dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole.		

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

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 exposure 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. [HA697 trade name] should only be used in pregnancy if the benefit clearly outweighs the risk.

Breast-feeding

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

Fertility

Animal studies have shown no effects on fertility. No human data on the effect of lopinavir/ritonavir 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. Nevertheless, the clinical status of the patient and adverse reactions of [HA697 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The most common adverse reaction associated with [HA697 trade name] therapy is diarrhoea, nausea and vomiting, usually at the start of treatment. Also, dyslipidaemia, including hypertriglyceridaemia and hypercholesterolaemia is common and may require drug treatment or discontinuation of the tablet.

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

The undesirable effects of [HA697 trade name] are listed below. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Infections and infestations	
Very common	Upper respiratory-tract infection
Common	Lower respiratory-tract infection, skin infections including cellulitis, folliculitis and furuncle
Blood and lymphatic system disorders	
Common	Anaemia, leucopenia, neutropenia, lymphadenopathy
Immune system disorders	
Common	Hypersensitivity including urticaria and angioedema
Uncommon	Immune reconstitution inflammatory syndrome
Endocrine disorders	
Uncommon	Hypogonadism
Metabolism and nutrition disorders	
Common	Blood glucose disorders including diabetes mellitus, hypertriglyceridaemia, hypercholesterolemia, weight decreased, decreased appetite
Uncommon	Weight increased, increased appetite
Psychiatric disorders	
Common	Anxiety
Uncommon	Abnormal dreams, libido decreased
Nervous system disorders	
Common	Headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, insomnia
Uncommon	Cerebrovascular accident, convulsion, dysgeusia, ageusia, tremor
Eye disorders	
Uncommon	Visual impairment
Ear and labyrinth disorders	
Uncommon	Tinnitus, vertigo
Cardiac disorders	
Uncommon	Atherosclerosis such as myocardial infarction, atrioventricular block, tricuspid valve incompetence
Vascular disorders	
Common	Hypertension
Uncommon	Deep-vein thrombosis
Gastrointestinal disorders	
Very common	Diarrhoea, nausea
Common	Pancreatitis (see section 4.4: pancreatitis and lipids), vomiting, gastro-oesophageal reflux disease, gastroenteritis and colitis, abdominal pain (upper and lower), abdominal distension, dyspepsia, haemorrhoids, flatulence
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 seborrhoeic dermatitis, night sweats, pruritus
Uncommon	Alopecia, capillaritis, vasculitis
Rare	Steven-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

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.

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

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

Paediatric populations

In children 2 years of age and older, the nature of the safety profile is similar to that seen in adults.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

For reporting of adverse events and PV related queries please write to Email: ProductSafety@viatris.com

4.9 Overdose

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

Symptoms

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

Therapy

There is no specific antidote for overdose with [HA697 trade name]. Treatment of overdose with [HA697 trade name] is general supportive measures including monitoring of vital signs and observation of the clinical status of the patient

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: antivirals for systemic use, antivirals for treatment of HIV infections, combinations, ATC code: J05AR10

Mechanism of action: Lopinavir provides the antiviral activity of [HA697 trade name]. Lopinavir inhibits the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

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

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

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

The in vitro antiviral activity of lopinavir against 112 clinical isolates taken from patients failing therapy with one or more protease inhibitors was assessed. Within this panel, the following mutations in the HIV protease were associated with reduced in vitro susceptibility to lopinavir: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M. The median EC_{50} of lopinavir against isolates with 0–3, 4–5, 6–7 and 8–10 mutations at the above amino acids was 0.8, 2.7, 13.5 and 44-fold higher than the EC_{50} against wild-type HIV, respectively. In addition to the mutations described above, mutations V32I and I47A have been observed in rebound isolates with reduced lopinavir susceptibility form protease inhibitor-experienced patients receiving ritonavir-boosted lopinavir therapy.

In studies of PI-experienced, NNRTI-naïve patients receiving therapy including ritonavir-boosted lopinavir, efavirenz and NRTIs, plasma HIV-RNA < 400 copies was observed at 48 weeks in 93% (25/27), 73% (11/15) and 25% (2/8) of patients with < 10-fold, 10 to 40-fold and > 40-fold reduced susceptibility to lopinavir at baseline. In another study with a dataset from several clinical trials and cohorts, the changes in drug susceptibility associated with a 20% and 80% loss of predicted wild-type drug effect for lopinavir were 9.7- and 56-fold, respectively.

Clinically relevant resistance to lopinavir requires the accumulation of resistance mutations in the HIV protease. Several genotypic resistance algorithms have been proposed for the quantification of the degree of phenotypic resistance to lopinavir, and for predicting the clinical response to lopinavir in protease inhibitor

pre-treated patients. One of these, the lopinavir-ATU score, includes mutations at the following codons of the protease: 10, 20, 24, 33, 36, 47, 48, 54, 82 and 84.

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

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

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

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

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

Effects on the electrocardiogram: QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) differences in QTcF from placebo were 3.6 (6.3) and 13.1(15.8) for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily ritonavir-boosted lopinavir, respectively. The two regimens resulted in exposures on Day 3 that were approximately 1.5- and 3-fold higher than those with recommended once-daily or twice-daily lopinavir/ritonavir doses at steady state. No subject experienced an increase in QTcF of ≥ 60 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 after dosing. Maximum PR interval was 286 ms and no second- or third-degree heart block was observed (see section 4.4).

5.2 Pharmacokinetic properties

The absorption characteristics of [HA697 trade name] have been determined after administration of single dose granules in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**	
	Lopinavir	**Ritonavir**
Maximum concentration (C_{max})	482 (± 328) ng/mL	31 (± 16) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	4490 (± 3584)ng·h/mL	275 (± 160) ng·h/mL
Time to attain maximum concentration (Tmax)	5.46 (± 1.53) hours	4.89 (± 0.54) hours

Pharmacokinetics of lopinavir/ritonavir

<table>
<tr><th></th><th>Lopinavir</th><th>Ritonavir</th></tr>
<tr><td colspan="3">General</td></tr>
<tr><td></td><td>The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-1 infected patients; no substantial differences were observed between the two groups. Administrations 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-1 infected patients.</td><td></td></tr>
<tr><td colspan="3">Absorption</td></tr>
<tr><td>Absolute bioavailability</td><td>NA*</td><td>NA</td></tr>
<tr><td>Oral bioavailability</td><td>NA</td><td>NA</td></tr>
<tr><td>Food effect</td><td><table><tr><th></th><th>$AUC_{(0-\infty)}$</th><th>C_{max}</th></tr><tr><td>Moderate fat:</td><td>27%↑</td><td>18%↑</td></tr><tr><td>High fat:</td><td>19%↑</td><td>↔</td></tr></table></td><td><table><tr><th></th><th>AUC</th><th>C_{max}</th></tr><tr><td>Moderate or high fat meal</td><td>20-23%↓↑</td><td>20-23%↓↑</td></tr></table></td></tr>
<tr><td colspan="3">Distribution</td></tr>
<tr><td>Volume of distribution (Vd/F; mean)</td><td>16.9 L</td><td>20–40L (after a single 600 mg dose)</td></tr>
<tr><td>Plasma proteinbindingin vitro</td><td>98-99%</td><td>98–99%</td></tr>
<tr><td>Tissue distribution</td><td>Cervicovaginal fluid: Lopinavir has been detected in cerebrospinal fluid at concentrations exceeding the IC_{50} of wild-type virus and has been shown to reduce HIV-RNA in cerebrospinal fluid.</td><td>Distributes to the cerebrospinal fluid and semen</td></tr>
<tr><td colspan="3">Metabolism</td></tr>
<tr><td></td><td>Lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. Lopinavir M1, M3, and M4 being the predominant metabolites found in plasma.</td><td>Extensively metabolised mainly by CYP3A and by CYP2D6</td></tr>
<tr><td>Active metabolite(s)</td><td>none</td><td>none</td></tr>
<tr><td colspan="3">Elimination</td></tr>
<tr><td>Elimination half life</td><td>5–6 h</td><td>5 h (100 mg twice daily or once daily)</td></tr>
<tr><td>Mean systemic clearance (Cl/F)</td><td>6–7 L/h</td><td>17 ± 7 L/h (100 mg once daily dose)</td></tr>
</table>

% of dose excreted in urine	10% (3% excreted unchanged)	11.3% (3.5% unchanged drug)
% of dose excreted in faeces	83% (19.8% excreted unchanged)	86% (34% unchanged drug)
Transporters	NA	Substrate for P-gp, MRP1. May inhibit P-gp, MRP, OATP-c an BCRP
Metabolizing enzymes	CYP3A	Substrate for CYP3A and CYP2D6. May inhibit CYP3A4 and 2D6 and induce CYP1A2, 2C8, 2C9, 2C19 and glucuronidation.

*NA : information not available

Special populations

Paediatrics: There are limited pharmacokinetic data in children below 2 years of age.

Gender, race and age: Lopinavir/ritonavir pharmacokinetics have not been studied in the elderly. No age-, gender- or race-related effect has been observed in adult patients.

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

5.3 Preclinical safety data

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

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

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

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

In rats, embryofetotoxicity (pregnancy loss, decreased fetal viability, decreased fetal body weights, increased

frequency of skeletal variations) and postnatal developmental toxicity (decreased survival of pups) was observed at maternally toxic dosages. The systemic exposure to lopinavir/ritonavir at the maternal and developmental toxic dosages was lower than the intended therapeutic exposure in humans.

Long-term carcinogenicity studies of lopinavir/ritonavir in mice revealed a non-genotoxic, mitogenic induction of liver tumours, generally considered to have little relevance to human risk.

Carcinogenicity studies in rats revealed no tumorigenic findings. Lopinavir/ritonavir was not found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone,

Sorbitan monolaurate,

Colloidal silicon dioxide,

Ethyl cellulose,

Mannitol,

Acesulfame potassium,

Sodium stearyl fumarate and

Vanilla flavour

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per sachet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Sachets, comprises of printed triple laminated roll with aluminium foil, soft, dull side PET and bright side laminated to PE film. 1000 mg granules per sachet.

Pack size: 120 sachets per carton

6.6 Special precautions for disposal and other handling

Preparation and administration - extemporaneous formulation for children

[HA697 trade name] should be mixed with soft food such as applesauce or porridge, or with a liquid such as water, before being taken. It should not be chewed or crushed.

For infants and young children who are able to take soft foods:

1. Work out the number of sachets needed for the correct dose.
2. Gently tap the sachets to ensure all the granules are at the bottom of the sachets, so they are not lost when opening.
3. Completely tear or cut off the top of the sachets so that the sachets are fully open.
4. Mix with the chosen material:

- **soft food** such as applesauce or porridge:
    - Place the food (approximately 1 teaspoon of soft food for each sachet) into a small clean cup or bowl.
    - Sprinkle the full contents of the sachet onto the food. Make sure no granules/powder are left inside the sachets.
    - Using a spoon, mix the contents of the sachet into the food.
    - Give or take all of the mixture. If any granules are left in the small cup/bowl or spoon, add more soft food to the granules and mix. Then give or take the mixture along with adequate drinking water, to ensure that no granules are left behind in the mouth.
- Mixing with **liquid** such as drinking water:
    - Add the appropriate amount of clean drinking water into a cup or bowl (1 teaspoon of water for 2 sachets; 2 teaspoons of water for 3 to 8 sachets; 3 teaspoons or 1 tablespoon for 10 sachets).
    - Sprinkle the entire contents of the sachets into the water and stir gently with a spoon to mix. Make sure no granules/powder are left inside the sachets.
    - Give or take all of the mixture. If any granules are left in the spoon, add a little more liquid (water) and mix. Then give or take the additional mixture.

5. The mixture must be made up freshly each time and used straight away. It must not be stored. Throw away any unused mixture.

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

1. Work out the number of sachets needed for the correct dose.
2. Gently tap the sachets to ensure all the granules are at the bottom of the sachets, so they are not lost when opening.
3. Completely tear or cut off the top of the sachets so that the sachets are fully open.
4. Add the granules to a small volume of expressed breast milk or formula in a spoon and give to the infant, or put the granules directly on the infant's tongue before breastfeeding. It is important to limit the amount of breast milk (or formula) used to an amount the infant is able to easily consume (2 or 3 teaspoons).
5. Give some additional breast milk (or formula) to make sure the infant has taken the entire dose of granules
6. The mixture must be made up freshly each time and used straight away. It must not be stored. Throw away any unused mixture

7. SUPPLIER

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad-500096
Telangana
India
Email: ProductSafety@viatris.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA697

9. DATE OF PREQUALIFICATION

27 October 2020

10. DATE OF REVISION OF THE TEXT

May 2024

References

Kaletra 100 mg/25 mg film-coated tablets, 100 mg/25 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 13 October 2022 (https://www.ema.europa.eu/en/documents/product-information/kaletra-epar-product-information_en.pdf, accessed 18 September 2023).

WHO Consolidated Guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021. (https://www.who.int/publications/i/item/9789240031593, accessed 18 September 2023).

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products