PROFESSIONAL INFORMATION FOR

LOPIMUNE 40/10 ORAL PELLETS

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

LOPIMUNE 40/10 ORAL PELLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of oral pellets contains lopinavir 40 mg and ritonavir 10 mg as active ingredients.

Sugar free.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

CAPSULE (ORAL PELLETS**)**

White to off white, circular biconvex pellets, plain on both sides filled in size "1" hard gelatin capsules having clear transparent body with '414' printed in black ink and yellow cap with 'CL' printed in black ink.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

LOPIMUNE 40/10 ORAL PELLETS are indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection in adults and children 6 months and older, weighing over 6 kg.

The choice of LOPIMUNE 40/10 ORAL PELLETS to treat protease inhibitor-experienced HIV-1 infected patients should be based on individual viral resistance testing and their treatment history (see **sections 4.4** and **5.1**).

4.2 Posology and method of administration

Posology

- LOPIMUNE 40/10 ORAL PELLETS should be initiated by a health care provider experienced in the management of HIV infection.
- LOPIMUNE 40/10 ORAL PELLETS should be given in a twice daily (every 12 hours) dosing regimen. LOPIMUNE 40/10 ORAL PELLETS should not be administered once daily (every 24 hours) to children < 18 years of age.
- LOPIMUNE 40/10 ORAL PELLETS should not be administered to premature neonates (born one month or more before expected date of delivery) until 14 days after their due date.
- LOPIMUNE 40/10 ORAL PELLETS administered in combination with efavirenz, nevirapine, or nelfinavir inpatients younger than 6 months of age is not recommended. Total dose of lopinavir and ritonavir oral pellets in paediatric patients should not exceed the recommended adult daily dose of 400/100 mg twice daily.

The recommended dose of LOPIMUNE 40/10 ORAL PELLETS for children is as follows:

Child's weight	Dose
6 – 9,9 kg	3 capsules twice daily (lopinavir 120 mg/ritonavir 30 mg twice daily)

10 – 13,9 kg	4 capsules twice daily (lopinavir 160 mg/ritonavir 40 mg twice daily)
14 – 19,9 kg	5 capsules twice daily (lopinavir 200 mg/ritonavir 50 mg twice daily)
20 – 24,9 kg	6 capsules twice daily (lopinavir 240 mg/ritonavir 60 mg twice daily)

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

Special populations

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. LOPIMUNE 40/10 ORAL PELLETS 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

For oral administration.

LOPIMUNE 40/10 ORAL PELLETS must be taken with a meal twice daily. LOPIMUNE 40/10 ORAL PELLETS should be sprinkled / mixed with soft food such as applesauce or porridge, or mixed with liquid such as water, as described below. LOPIMUNE 40/10 ORAL PELLETS should not be chewed or crushed**.**

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

1. Determine the number of capsules needed to prepare a dose.

2. Prior to mixing, tap the capsules to move all the pellets to the bottom of the capsules

3. Mixing with soft food such as applesauce or porridge: Twist the ends of the capsule in opposite direction and pull apart so that the entire contents of the capsule are sprinkled over the soft food. Repeat this step for the prescribed number of capsules per dose. Using a spoon, mix the entire contents of the LOPIMUNE 40/10 ORAL PELLETS with soft food (approximately 1 teaspoon of soft food for 1 capsule; 2 teaspoons for 2 capsules etc.) in a small cup or bowl. Make sure no pellets are left inside the capsules. Give or take all of the mixture. If any pellets are left in the small cup/bowl or spoon, add more soft food to the pellets and mix. Then give or take the mixture along with adequate drinking water, to ensure that no pellets are left behind in the mouth.

4. Mixing with liquid such as drinking water: Mix the entire contents of LOPIMUNE 40/10 ORAL PELLETS with approximately 5 - 15 ml of drinking water (1 teaspoon of water for 2 capsules; 2 teaspoons of water for 3 to 8 capsules; 3 teaspoons or 1 tablespoon for 10 capsules). Make sure no pellets/powder are left inside the capsules. Give or take all of the mixture. If any pellets are left in the spoon, add more liquid (water) and mix. Then give or take the mixture.

5. Administer the medicine/food mixture within 2 hours of preparation. If not administered within 2 hours of preparation, throw away the mixture and prepare a new dose.

6. No mixture of the pellets and food is to be stored for later use.

7. Repeat above steps for next dose.

4.3 Contraindications:

- LOPIMUNE 40/10 ORAL PELLETS are contraindicated in patients with known hypersensitivity to lopinavir, ritonavir or any other ingredients of LOPIMUNE 40/10 ORAL PELLETS. (see **section 6.1**).
- Must not be administered in patients with severe hepatic insufficiency as LOPIMUNE 40/10 ORAL PELLETS have not been studied in this condition.
- LOPIMUNE 40/10 ORAL PELLETS should not be co-administered with medicines with a narrow therapeutic window that are substrates of the isoenzyme CYP3A4, such as alfuzosin, amiodarone, dronedarone, bepridil, quinidine, propafenone, verapamil, lurasidone, pimozide, quetiapine, astemizole, terfenadine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir (with or without dasabuvir), oral midazolam, triazolam, clorazepate, diazepam, flurazepam, ergot derivatives, fusidic acid, venetoclax, colchicine, simvastatin and lovastatin, avanafil, sildenafil vardenafil (non-exhaustive list). Inhibition of CYP3A4 by ritonavir could increase plasma concentrations of these medicines, 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 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: LOPIMUNE 40/10 ORAL PELLETS 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 medicine information for these medicines.

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 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. 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 LOPIMUNE 40/10 ORAL PELLETS 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 medicines 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 LOPIMUNE 40/10 ORAL PELLETS therapy should be suspended if pancreatitis is diagnosed (see **section 4.8**).

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

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

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency, typically in the first few weeks or months after initiation of combination antiretroviral treatment, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

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

PR interval prolongation: Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. 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 medicines that prolong the PR interval (such as verapamil or atazanavir). LOPIMUNE 40/10 ORAL PELLETS should be used with caution in such patients (see **sections 4.8, 5.1 and 5.3**).

Warnings on specific interactions with other medicines

LOPIMUNE 40/10 ORAL PELLETS contains ritonavir, which is a very potent inhibitor of the P450 isoform CYP3A. LOPIMUNE 40/10 ORAL PELLETS is likely to increase plasma

concentrations of medicines that are primarily metabolised by CYP3A. These increases of plasma concentrations of co-administered medicines could increase or prolong their therapeutic effect and adverse events (see **sections 4.3 and 4.5**).

Bedaquiline and delamanid: Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with lopinavir/ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with lopinavir/ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see **section 4.5** and refer to the bedaquiline SmPC). Co-administration of delamanid with a strong inhibitor of CYP3A (as lopinavir/ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **section 4.5** and refer to the delamanid professional information).

Rifampicin: Co-administration of LOPIMUNE 40/10 ORAL PELLETS with rifampicin is not recommended. Rifampicin in combination with LOPIMUNE 40/10 ORAL PELLETS causes large decreases in lopinavir concentrations which may in turn significantly decrease the therapeutic effect of lopinavir. Adequate exposure to lopinavir/ritonavir may be achieved with a higher dose of LOPIMUNE 40/10 ORAL PELLETS but this is associated with a higher risk of liver and gastrointestinal toxicity.

HMG-CoA reductase inhibitors: Simvastatin and lovastatin are highly dependent on CYP3A for metabolism; thus concomitant use of LOPIMUNE 40/10 ORAL PELLETS and simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis.

Caution must also be exercised and reduced doses should be considered if LOPIMUNE 40/10 ORAL PELLETS is used concurrently with rosuvastatin or with atorvastatin, which are metabolised to a lesser extent by CYP3A4. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or □luvastatin 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 LOPIMUNE 40/10 ORAL PELLETS. Co-administration of LOPIMUNE 40/10 ORAL PELLETS with these medicines 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 LOPIMUNE 40/10 ORAL PELLETS is contraindicated (see **section 4.3**).

QT-interval prolonging medicines: Particular caution must be used when prescribing LOPIMUNE 40/10 ORAL PELLETS and medicines that prolong QT interval such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. LOPIMUNE 40/10 ORAL PELLETS could increase concentrations of the co-administered medicines 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 LOPIMUNE 40/10 ORAL PELLETS cannot be currently ruled out (see **sections 4.8 and 5.3**).

Sedative medicines: LOPIMUNE 40/10 ORAL PELLETS should not be used concomitantly with strongly sedative medicines metabolised by CYP3A, as this may result in excessive effects. Such medicines include fentanyl, meperidine, propoxyphene, diazepam, alprazolam, triazolam and midazolam. Morphine and oxazepam are not metabolised by CYP3A; however, due to

induction of glucuronidation, an increased dose of these medicines may be necessary when co-treating with LOPIMUNE 40/10 ORAL PELLETS.

Hormonal contraceptives: In case of co-administration of LOPIMUNE 40/10 ORAL PELLETS with contraceptives containing ethinylestradiol, irrespective of the formulation (e.g. oral or patch), additional barrier or non-hormonal methods of contraception are to be used. The decreased systemic exposure to the oestrogen component may not only reduce contraceptive efficacy but also alter the uterine bleeding profile.

Glucocorticoids: Concomitant use of LOPIMUNE 40/10 ORAL PELLETS and fluticasone or other glucocorticoids that are metabolised by CYP3A4 such as budesonide and fluticasone, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see **section 4.5**).

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

Tadalafil: Co-administration of LOPIMUNE 40/10 ORAL PELLETS with tadalafil, indicated for the treatment of pulmonary arterial hypertension, is not recommended. (**See section 4.5**).

Fusidic acid: Co-administration of LOPIMUNE 40/10 ORAL PELLETS with fusidic acid in osteo-articular infections is not recommended (see **section 4.5**).

Salmeterol: Co-administration of LOPIMUNE 40/10 ORAL PELLETS with salmeterol is not recommended (see **section 4.5**).

Rivaroxaban: Co-administration of LOPIMUNE 40/10 ORAL PELLETS with rivaroxaban is not recommended (see **section 4.5**).

Vorapaxar: Co-administration of LOPIMUNE 40/10 ORAL PELLETS with vorapaxar is not recommended. (See **section 4.5**).

Riociguat: Co-administration of LOPIMUNE 40/10 ORAL PELLETS with riociguat is not recommended. (See **section 4.5**).

Transmission

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

People taking LOPIMUNE 40/10 ORAL PELLETS may still develop infections or other illnesses associated with HIV disease and AIDS.

4.5 Interaction with other medicines and other forms of interaction

LOPIMUNE 40/10 ORAL PELLETS contains lopinavir and ritonavir, both of which inhibit the P450 isoform CYP3A *in vitro*. Co-administration of LOPIMUNE 40/10 ORAL PELLETS and medicines primarily metabolised by CYP3A may increase plasma concentrations of the other medicines, which could increase or prolong its therapeutic and adverse reactions (see **section 4.3**). LOPIMUNE 40/10 ORAL PELLETS 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 medicines metabolised by cytochrome P450 (including CYP2C9 and CYP2C19) enzymes and by glucuronidation. This may lower plasma concentrations and potentially decrease efficacy of co-administered medicines. Medicines that are contraindicated

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

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
HIV-1 antivirals		
HIV-1 protease inhibitor: fosamprenavir/ritonavir	Lowered amprenavir and lopinavir concentrations.	An increased rate of adverse reactions has been observed with co-administration of these medicines.
HIV-1 protease inhibitor: indinavir	Increased indinavir concentration.	Decrease indinavir dose to 600 mg twice daily, when co-administered with lopinavir/ritonavir 400/100 twice daily. Lopinavir/ritonavir once daily has not been studied in combination with indinavir.
HIV-1 protease inhibitor: nelfinavir	Increased concentrations of nelfinavir and m8 metabolite of nelfinavir. Lowered lopinavir concentration.	Lopinavir/ritonavir once daily in combination with nelfinavir is not recommended.
HIV-1 protease inhibitor: ritonavir	Increased lopinavir concentration.	Appropriate doses of additional ritonavir in combination with

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		LOPIMUNE 40/10 ORAL PELLETS have not been established.
HIV-1 protease inhibitor: saquinavir	Increased saquinavir concentration.	The saquinavir dose is 1000 mg twice daily, when co-administered with lopinavir/ritonavir 400/100 mg twice daily. Lopinavir/ritonavir once daily has not been studied in combination with saquinavir.
HIV CCR5 – antagonist: maraviroc	Increased maraviroc concentrations.	When co-administered, patients should receive 150 mg twice daily of maraviroc. For further details see complete prescribing information for maraviroc.
Non-nucleoside reverse transcriptase inhibitors: efavirenz and nevirapine	Lowered lopinavir concentrations.	The dose of lopinavir/ritonavir should be increased when co-administered with efavirenz or nevirapine.
Nucleoside reverse transcriptase inhibitor: didanosine	-	It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		hour before or two hours after LOPIMUNE 40/10 ORAL PELLET**S** (given with food).
Nucleoside reverse transcriptase inhibitor: tenofovir disoproxil fumarate	Increased tenofovir concentrations.	Patients receiving LOPIMUNE 40/10 ORAL PELLETS and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside reverse transcriptase inhibitors: abacavir and zidovudine	Lowered concentrations of abacavir and zidovudine.	The clinical significance of this potential interaction is unknown.
Other medicines		
Antidysrhythmics e.g. amiodarone and lidocaine (systemic)	Increased concentrations of antidysrhythmics.	See '**CONTRAINDICATIONS'** for contraindicated antidysrhythmics. Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antidysrhythmics when co-administered with LOPIMUNE 40/10 ORAL PELLETS.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
Anticancer medicines: vincristine, vinblastine, dasatinib, nilotinib	Increased concentrations of anticancer medicines.	For vincristine and vinblastine, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as LOPIMUNE 40/10 ORAL PELLETS. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.
Anticoagulants: warfarin and rivaroxaban	Increased or decreased warfarin concentrations.	Concentrations of warfarin may be affected. Initial frequent monitoring of the INR (international normalised ratio) during LOPIMUNE 40/10 ORAL PELLETS and warfarin co-

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
	Increased rivaroxaban concentrations.	administration is recommended. Avoid concomitant use of rivaroxaban and LOPIMUNE 40/10 ORAL PELLETS. Co-administration of LOPIMUNE 40/10 ORAL PELLETS and rivaroxaban may lead to increased risk of bleeding.
Anticonvulsants: carbamazepine, phenobarbitone, phenytoin	Lowered lopinavir and phenytoin concentrations.	LOPIMUNE 40/10 ORAL PELLETS may be less effective due to decreased lopinavir concentrations in patients taking these medicines concomitantly and should be used with caution. LOPIMUNE 40/10 ORAL PELLETS once daily in combination with carbamazepine, phenobarbitone, or phenytoin is not recommended. In addition, co-administration of phenytoin and LOPIMUNE 40/10 ORAL PELLETS may cause decreases

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with LOPIMUNE 40/10 ORAL PELLETS.
Anticonvulsants: lamotrigine, valproate	Lowered lamotrigine concentrations. Valproate concentrations may be lowered or remain unchanged.	A dose increase of lamotrigine or valproate may be needed when co-administered with LOPIMUNE 40/10 ORAL PELLETS and therapeutic concentration monitoring for lamotrigine may be indicated, particularly during dosage adjustments.
Antidepressant: bupropion	Lowered concentrations of bupropion and its active metabolite, hydroxybupropion.	Patients receiving LOPIMUNE 40/10 ORAL PELLETS and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	Increased trazodone concentrations.	Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		trazodone and ritonavir. A lower dose of trazodone should be considered.
Anti-infective: clarithromycin	Increased clarithromycin concentrations.	For patients with renal impairment, adjust clarithromycin dose.
Antifungals: ketoconazole, itraconazole and voriconazole	Increased concentrations of ketoconazole and itraconazole. Lowered concentrations of voriconazole.	High doses of ketoconazole (>200 mg/day) or itraconazole (> 200 mg/day) are not recommended. The co-administration of voriconazole and LOPIMUNE 40/10 ORAL PELLETS should be avoided. Alternative antifungal therapies should be considered in these patients.
Anti-gout: colchicine	Increased concentrations of colchicine.	Concomitant administration with colchicine is contraindicated in patients with renal and/or hepatic impairment (see

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		'**CONTRAINDICATIONS**').
Antimycobacterial: rifabutin	Increased concentrations of rifabutin and its metabolite.	Dosage reduction of rifabutin may be necessary.
Antiparasitic: atovaquone	Lowered concentrations of atovaquone.	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Antipsychotics: quetiapine	Increased concentrations of quetiapine.	Initiation of LOPIMUNE 40/10 ORAL PELLETS in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures.
Sedative/ hypnotics: parenterally administered midazolam	Increased midazolam concentrations.	See '**CONTRAINDICATIONS'** for contraindicated sedatives/ hypnotics.
Contraceptive: ethinyl estradiol	Lowered concentrations of ethinyl estradiol.	Because contraceptive steroid concentrations may be altered when LOPIMUNE 40/10 ORAL PELLETS are co-administered with oral contraceptives or with the contraceptive patch,

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		alternative methods of nonhormonal contraception are recommended.
Corticosteroids (systemic): e.g. budesonide, dexamethasone, prednisone	Increased concentrations of glucocorticoids and decreased concentrations of lopinavir.	Use with caution. LOPIMUNE 40/10 ORAL PELLETS may be less effective due to decreased lopinavir plasma concentrations in patients taking these medicines concomitantly.
Dihydropyridine calcium channel blockers: e.g. felodipine and nifedipine	Increased concentrations of dihydropyridine calcium channel blockers.	Clinical monitoring of patients is recommended and a dose reduction of the dihydropyridine calcium channel blocker may be considered.
HMG-CoA reductase inhibitors: atorvastatin and rosuvastatin	Increased concentrations of atorvastatin and rosuvastatin.	See '**CONTRAINDICATIONS'** for contraindicated HMG-CoA reductase inhibitors.
Immunosuppressants: e.g. ciclosporin, tacrolimus and sirolimus	Increased concentrations of immunosuppressants.	Therapeutic concentration monitoring is recommended for immunosuppressant medicines when co-administered with

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		LOPIMUNE 40/10 ORAL PELLETS.
Inhaled or intranasal steroids e.g.: fluticasone and budesonide	Increased concentrations of glucocorticoids.	Concomitant use of LOPIMUNE 40/10 ORAL PELLETS and fluticasone or other glucocorticoids that are metabolised by CYP3A is not recommended.
Long-acting beta-adrenoceptor agonist: salmeterol	Increased concentrations of salmeterol.	Concurrent administration of salmeterol and LOPIMUNE 40/10 ORAL PELLETS is not recommended.
Narcotic analgesics: methadone and fentanyl	Decreased concentrations of methadone and increased concentrations of fentanyl.	Dosage of methadone may need to be increased when co-administered with LOPIMUNE 40/10 ORAL PELLETS. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with LOPIMUNE

Concomitant medicine class: name of medicine	Effect on concentration of lopinavir or concomitant medicine	Clinical comments
		40/10 ORAL PELLETS.
PDE5 inhibitors: sildenafil, tadalafil and vardenafil	Increased concentrations of sildenafil, tadalafil and vardenafil.	Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): sildenafil is contraindicated.

4.6 Fertility, pregnancy and lactation:

Pregnancy

The safety of LOPIMUNE 40/10 ORAL PELLETS in pregnant women has not been established, as there are no adequate and well-controlled studies in pregnant women. The use of LOPIMUNE 40/10 ORAL PELLETS during pregnancy is not recommended.

Breastfeeding

HIV-infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving LOPIMUNE 40/10 ORAL PELLETS. It is not known whether lopinavir is secreted in human milk.

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 LOPIMUNE 40/10 ORAL PELLETS should be borne in mind when considering the patient's ability to drive or operate machinery. \

4.8 Undesirable effects

a) Summary of adverse effects

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

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

b) Tabulated summary of adverse reactions

The following adverse reactions of moderate to severe intensity with possible or probable relationship to lopinavir/ritonavir have been reported. The adverse reactions are displayed by system organ class. Events shown with a frequency Unknown were identified during post-marketing surveillance.

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Frequent	Upper respiratory-tract infection

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
	Frequent	Lower respiratory-tract infection, skin infections including cellulitis, folliculitis and furuncle
Blood and lymphatic system disorders	Frequent	Anaemia, leucopenia, neutropenia, lymphadenopathy
Immune system disorders	Frequent	Hypersensitivity including urticaria and angioedema
	Less frequent	Immune reconstitution inflammatory syndrome
Endocrine disorders	Less frequent	Hypogonadism
Metabolism and nutrition disorders	Frequent	Blood glucose disorders including diabetes mellitus, hypertriglyceridaemia, hypercholesterolemia, weight decreased, decreased appetite
	Less frequent	Weight increased, increased appetite
Psychiatric disorders	Frequent	Anxiety
	Less frequent	Abnormal dreams, libido decreased
Nervous system disorders	Frequent	Headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, insomnia
	Less frequent	Cerebrovascular accident, convulsion, dysgeusia, ageusia, tremor
Eye disorders	Less frequent	Visual impairment
Ear and labyrinth disorders	Less frequent	Tinnitus, vertigo
Cardiac disorders	Less frequent	Atherosclerosis such as myocardial infarction, atrioventricular block, tricuspid valve incompetence
Vascular disorders	Frequent	Hypertension
	Less frequent	Deep-vein thrombosis
Gastrointestinal disorders	Frequent	Diarrhoea, nausea

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
	Frequent	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
	Less frequent	Gastrointestinal haemorrhage including gastrointestinal ulcer, duodenitis, gastritis and rectal haemorrhage, stomatitis and oral ulcers, faecal incontinence, constipation, dry mouth
Hepatobiliary disorders	Frequent	Hepatitis including AST, ALT and GGT increases Hepatic steatosis, hepatomegaly, cholangitis, hyperbilirubinemia
	Less frequent	Jaundice
	Frequency unknown	
Skin and subcutaneous tissue disorders	Frequent	Rash including maculopapular rash, dermatitis/rash including eczema and seborrheic dermatitis, night sweats, pruritus
	Less frequent	Alopecia, capillaritis, vasculitis
	Frequency unknown	Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	Frequent	Myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such as weakness and spasms
	Less frequent	Rhabdomyolysis, osteonecrosis
Renal and urinary disorders	Less frequent	Creatinine clearance decreased, nephritis, haematuria
Reproductive system and breast disorders	Frequent	Erectile dysfunction, menstrual disorders - amenorrhoea, menorrhagia

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
General disorders and administration site conditions	Frequent	Fatigue including asthenia

c) 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.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see **section 4.4**).

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Therapy

Treatment of overdose with LOPIMUNE 40/10 ORAL PELLETS should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with LOPIMUNE 40/10 ORAL PELLETS. If indicated, elimination of unabsorbed medicine should be achieved by emesis. Administration of activated charcoal may also be used to aid in removal of unabsorbed medicine. Since LOPIMUNE 40/10 ORAL PELLETS are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Anti-viral agents

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

Mechanism of action: Lopinavir provides the antiviral activity of Lopinavir/Ritonavir Pellets for Oral suspension 40 mg/10 mg. 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 IC50 of lopinavir against five different HIV-1 laboratory strains was 19 nM. In the absence and presence of 50 % human serum, the mean IC50 of lopinavir against HIV-1IIIB in MT4 cells was 17 nM and 102 nM, respectively. In the absence of human serum, the mean IC50 of lopinavir was 6,5 nM against several HIV-1 clinical isolates. Lopinavir also has *in vitro* activity against HIV-2, with median IC50 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, 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 EC50 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 EC50 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 medicine susceptibility associated with a 20 % and 80 % loss of predicted wild-type medicine effect for lopinavir were 9,7- and 56-fold, respectively.

Clinically relevant resistance to lopinavir requires accumulation of resistance mutations in the HIV-protease. Several genotypic resistance algorithms have been proposed for the quantification of the degree of phenotypic resistance to lopinavir, and for predicting the clinical response to lopinavir in protease 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 professional information of these darunavir or tipranavir-containing medicines for information on genotypic predictors of response).

Table 1 Clinical cut-off values for 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 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving lopinavir/ritonavir in the same study on Day 3. The mean changes from baseline in PR interval ranged from 11,6 ms to 24,4 ms in the 12-hour interval after dosing. Maximum PR interval was 286 msec and no second- or third-degree heart block was observed (see **section 4.4)**.

5.2 Pharmacokinetic properties

The absorption characteristics of Lopinavir/Ritonavir Pellets for Oral suspension 40 mg/10 mg have been determined after administration of single dose pellets in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**	
	Lopinavir	**Ritonavir**
Maximum concentration (Cmax)	482 (± 328) ng/mL	31 (± 16) ng/mL
Area under the curve (AUC0–∞), a measure of the extent of absorption	4,490 (± 3,584) ng·h/mL	0,275 (± 0,160) ng·h/mL
Time to attain maximum concentration (Tmax)	5,46 (± 1,53) hours	4,89 (± 0,54) hours

Lopinavir is almost completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of ritonavir-boosted lopinavir 400/100 mg twice daily yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg twice daily. The *in vitro* antiviral EC50 of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Lopinavir/Ritonavir Pellets for Oral suspension 40 mg/10 mg 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.

Distribution

At steady state, lopinavir is approximately 98−99 % bound to serum proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. Lopinavir has been detected in cerebrospinal fluid at concentrations exceeding the IC50 of wild-type virus and has been shown to reduce HIV-RNA in cerebrospinal fluid.

Biotransformation

In vitro experiments indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor, which inhibits the metabolism of lopinavir and therefore increases plasma levels of lopinavir. At least 13 metabolites of lopinavir

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

Elimination

After administering radio-labelled lopinavir with ritonavir, approximately 10 % and 83 % of an administered dose was accounted for in urine and faeces, respectively. After multiple dosing, less than 3 % of the lopinavir dose is excreted unchanged in the urine. The effective (peak to trough) half-life of lopinavir over a 12-hour dosing interval averaged 5–6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6–7 litre/hour.

Special populations

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

INTRAGRANULAR INGREDIENTS:

Colloidal silicon dioxide, Copovidone, Sorbitan Monolaurate,.

LUBRICANTS:

Colloidal silicon dioxide, Sodium stearyl fumarate.

COATING:

Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol 6000, Talc,

Hard gelatin capsule shell Size ‘1’

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in the original container at or below 30 °C.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

6.5 Nature and contents of container

LOPIMUNE 40/10 ORAL PELLETS in capsules are packed in pack sizes of 120’s in white HDPE containers fitted with white HDPE lids, containing two 1 g silica gel desiccant.

6.6 Special precautions for disposal and other handling

No special precautions are required.

For detail instructions on administration of LOPIMUNE 40/10 ORAL PELLETS, see **section 4.2**.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

1474 South Coast Road

Mobeni

Durban

4052

8. REGISTRATION NUMBER(S):

51/20.2.8/0123

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 26 June 2019

Latest renewal: Not applicable

10. DATE OF REVISION OF THE TEXT

13 October 2025