Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg

1. NAME OF THE MEDICINAL PRODUCT
Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains:
Lopinavir USP…….40 mg
Ritonavir USP…….10 mg
This medicine contains mannitol (583 mg) per sachet.

3. PHARMACEUTICAL FORM

A white to creamish granular powder filled in sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Lopinavir/Ritonavir Oral Granules 40 mg / 10 mg is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 14 days and older.

The choice of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg to treat protease inhibitor-experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Lopinavir/Ritonavir Oral Granules 40 mg/10 mg should be prescribed by physicians who are experienced in the treatment of HIV infection**.**
In patients weighing <15 kg, the recommended dose is 12 mg lopinavir/3 mg ritonavir/kg BW given twice daily
In patients weighing 15-35 kg, the recommended dose is 10 mg lopinavir /2.5 mg ritonavir /kg BW given twice daily
In patients weighing > 35 kg, the adult dose of 400 mg lopinavir/100 mg ritonavir given twice daily should be used.

The following table contains dosing guidelines for Lopinavir/Ritonavir Oral Granules 40 mg/ 10 mg, in accordance with WHO guidelines.

Body weight	Recommended number of 40 mg/ 10 mg granule sachets	
	morning	evening
3.0–5.9 kg	2	2
6.0–9.9 kg	3	3
10.0–13.9 kg	4	4
14.0–19.9 kg	5	5
20.0–24.9 kg	6	6
25.0–29.9 kg	7	7
	Consider using pediatric formulation (lopinavir/ritonavir 100/25 mg) for older children who can	

	swallow tablets to avoid the need to administer a high number of Lopinavir/ritonavir granules	
30 - 34.9 kg	8	8
	Use pediatric formulation (lopinavir/ritonavir 100/25 mg) for older children who can swallow tablets to avoid the need to administer a high number of Lopinavir/ritonavir granules	
> 35 kg	10	10
	Consider using adult formulation (lopinavir/ritonavir 200/50 mg) for older children who can swallow tablets to avoid the need to administer a high number of Lopinavir/ritonavir granules	

In children co-treated with nevirapine or efavirenz the following doses should be used

For patients weighing <15 kg, 13/3.25 mg/kg should be given twice daily
For patients weighing >15 kg, 11/2.75 mg/kg should be given twice daily

The doses should be taken approximately 12 hours apart.

Children less than 14 days of age and premature neonates: Lopinavir/Ritonavir Granules 40 mg / 10 mg should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been reached (see section 4.4).
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. No data are available in patients with severe hepatic impairment. Lopinavir/Ritonavir Oral Granules 40 mg / 10 mg must not be given to these patients.

Renal impairment: No dose adjustment is necessary in patients with renal impairment. Caution is warranted when Granules 40 mg / 10 mg is used in patients with severe renal impairment.

HOW TO ADMINISTER LOPINAVIR/RITONAVIR ORAL GRANULES
Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg must be taken with a meal twice daily. Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg should be sprinkled/mixed with soft food such as applesauce or porridge, or mixed with liquid such as water, as described below. Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg should not be chewed or crushed.

Instructions for Mixing Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg
1. Determine the number of sachets needed to prepare a dose.
2. Prior to mixing, tap the sachet(s) to move all the granules to the bottom of the sachet(s).
3. Completely tear or cut off the top of the sachet(s) and make sure the sachet(s) are fully open.
4. Mixing with soft food such as applesauce or porridge: Using a spoon, mix the entire contents of the Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg sachet(s) with soft food (approximately 1 teaspoon of soft food for 1 sachet; 2 teaspoons for 2 sachets, etc.) in a small cup or bowl. Make sure no granules/powder are left inside the sachet(s). Give or take all of the mixture. If any granules are left in the small cup/bowl or spoon, add more soft food to the granules and mix. Then give or take the mixture along with adequate drinking water, to ensure that no granules are left behind in the mouth.
5. Mixing with liquid such as drinking water: Mix the entire contents of the Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg sachet(s) with approximately 5 - 15 ml of drinking water in a teaspoon/ tablespoon (1 teaspoon of water for 2 sachets; 2 teaspoons of water for 3 to 8 sachets; 3 teaspoons or 1 tablespoon for 10 sachets).

Make sure no granules/powder are left inside the sachet(s). Give or take all of the mixture. If any granules are left in the spoon, add more liquid (water) and mix. Then give or take the mixture.
6. Administer the drug/food mixture within 2 hours of preparation. If not administered within 2 hours of preparation, throw away the mixture and prepare a new dose.
7. Repeat above steps for next dose.

For infants not yet taking solid food, i.e. less than 6 months of age:
There is currently no experience administering granules to infants less than 3 months. In the youngest infants (3-6 months of age) in the CHAPAS 2 study, oral pellets were added to a small volume of expressed breastmilk in a spoon and given to the infant or administered directly on the infant's tongue prior to breastfeeding. Since oral granules should not be chewed or crushed prior to administration, it is important to ensure that infants are developmentally able to swallow them..

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

INFORMATION FOR HEALTHCARE PROVIDERS

- Adequate instructions must be provided to the caregiver or older child regarding administration of the oral granules to ensure the correct number of sachets are opened and the entire dose is administered as required.
- It may be useful to **DEMONSTRATE** how to administer the **FIRST** dose to the caregiver.
- If giving Lopinavir/ritonavir granules to infants < 6months it may also be helpful to **OBSERVE** administration of the first dose to ensure the infant swallows the full dose. Infants should be carefully observed for signs of aspiration which may include, coughing, choking, gagging or eye reddening.
- The reason why the granules should not be chewed to maintain the integrity of this dosage form, which is melt-extrusion matrix similar to Lopinavir/ritonavir 100mg/25mg heat-stable tablets, which, when crushed or broken may significantly decrease drug exposure.
- Therefore, the recommended soft food should be one that does not require chewing to minimize the chances of the child chewing the granules.
- Consider using Lopinavir/ritonavir oral liquid (refer SmPC of Lopinavir/ritonavir oral liquid for dosing instructions), for infants who are unable to swallow solid particles such as the granules.
- Consider using Lopinavir/ritonavir 100mg/25mg tablets (refer SmPC of Lopinavir/ritonavir 100mg/25mg tablets for dosing instructions), for older children who can swallow tablets to avoid the need to administer a high number of Lopinavir/ritonavir granules.

4.3 Contraindications

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

Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg must not be administered to patients with severe hepatic impairment.

Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg must not be administered concurrently with agents with a narrow therapeutic window that are substrates of CYP3A4, such as amiodarone, bepedril, quinidine, propafenone, verapamil, pimozide, astemizole, terfenadine, cisapride, triazolam, ergot derivatives, simvastatin and lovastatin (non-exhaustive list). Inhibition of CYP3A4 by ritonavir could result in elevated 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 co-existing conditions

Hepatic impairment: Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is contraindicated in patients with severe liver impairment (see section 4.3). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

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

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 had been evoked, although the mechanism of action had not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

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 testing is to be performed prior to initiating Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg therapy and at periodic intervals during therapy. Particular caution should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders are to be managed as clinically appropriate.

Pancreatitis: Cases of pancreatitis have been reported in patients receiving lopinavir and ritonavir. Most of these cases patients have had a prior history of pancreatitis and/or concurrent therapy with other medicinal products associated with pancreatitis. Marked triglyceride elevation is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in

laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg therapy should be suspended if a diagnosis of pancreatitis is made (see section 4.8).

Hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of existing 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.

Fat redistribution and metabolic disorders: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between protease inhibitors (PIs) and visceral lipomatosis, and between certain nucleoside reverse transcriptase inhibitors (NRTIs), mainly stavudine and zidovudine, and lipoatrophy, seems likely given available evidence. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Immune Reactivation Syndrome: In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, 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.

Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. So far, this disease 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, 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg should be used with caution in such patients (see sections 4.8, 5.1 and 5.3).

Toxicity in Preterm Neonates: Lopinavir/Ritonavir Oral Granules 40 mg/10 mg should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of Lopinavir/Ritonavir Oral Granules 40 mg/10 mg in this patient population has not been established. However, if the benefit of using Lopinavir/Ritonavir Oral Granules 40 mg/10 mg to treat HIV infection in infants immediately after birth outweighs the potential risks, infants should be monitored closely for increases in serum

osmolality and serum creatinine, and for toxicity related to Lopinavir/Ritonavir Oral Granules 40 mg/10 mg including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis.

Warnings on specific interactions with other medicinal products

Rifampicin: Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg with rifampicin is not recommended.
Rifampicin in combination with Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg 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 when a higher dose of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is used but this is associated with a higher risk of liver and gastrointestinal toxicity.

Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg contains ritonavir, which is a very potent inhibitor of the P450 isoform CYP3A. Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg 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).

HMG-CoA reductase inhibitors: Simvastatin and lovastatin are highly dependent on CYP3A for metabolism; thus concomitant use of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is used concurrently with rosuvastatin or with atorvastatin, which are metabolised to a lesser extent by CYP3A4. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

QT-interval prolonging agents: Particular caution must be used when prescribing Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and medicinal products known to induce QT interval prolongation. Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg could increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac adverse events (see also section 4.3 and 4.5).

Sedative agents: Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg should not be used concomitantly with strongly sedative drugs metabolized by CYP3A, as this may result in excessive effects. Such drugs include, among others, fentanyl, meperidine, propoxiphene, diazepam, alprazolam, triazolam and midazolam. Morphine and oxazepam are not metabolized by CYP3A; however, due to induction of glucuronidation, an increased dose of these drugs may be necessary when co-treating with Lopinavir/Ritonavir granules 40 mg/ 10 mg.

Hormonal contraceptives: In case of co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg with contraceptives containing ethinyl oestradiol, 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 estrogen component may not only impact the contraceptive efficacy but also lead to alterations in the uterine bleeding profile.

Glucocorticoids: Concomitant use of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended

unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Other

Treatment with Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer. Patients should continue to use appropriate precautions to prevent transmission of HIV.

People taking Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg may still develop infections or other illnesses associated with HIV disease and AIDS.

4.5 Interactions with other medicinal products and other forms of interaction

Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A *in vitro*. Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse reactions. Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

Lopinavir/ritonavir has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some medicinal products metabolised by cytochrome P450 enzymes and by glucuronidation. This may result in lowered plasma concentrations and potential decrease of efficacy of co-administered medicinal products. Medicinal products that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in section 4.3.

All interaction studies, when not stated otherwise, were performed using lopinavir/ritonavir capsules (Kaletra®) at the dose of 400/100 mg b.i.d.

The following list of drug interactions with Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is not exhaustive, but is a selection of interactions of putative importance.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
Stavudine	Not studied, but no interaction expected	No dose adjustment necessary.
Lamivudine	Not studied, but no interaction expected	No dose adjustment necessary.
Emtricitabine	Not studied, but no interaction expected	No dose adjustment necessary.
Zidovudine	No clinically relevant interaction expected	No dose adjustment necessary.
Abacavir (600 mg q.d.)	Abacavir AUC ↓ 30%	No dose adjustment recommended.
Tenofovir (300 mg q.d.)	Tenofovir AUC ↑ 30%	No dose adjustment recommended. Renal function should be monitored.

Efavirenz (600 mg q.d./ lopinavir/ritonavir tablets 400/100 b.i.d)	Lopinavir AUC ↓ 30-40%	In adults, a 25% dose increase of lopinavir/ritonavir is recommended. For dosing in children when co-administering efavirenz.
Nevirapine (200 mg b.i.d)	Lopinavir AUC ↓ 27%, C_{min} ↓ 51% compared to historical data	In adults, a 25% dose increase of lopinavir/ritonavir is recommended. For dosing in children when co-administering nevirapine.
Etravirine (1600 mg b.i.d.)	Lopinavir AUC ↓ 20% Etravirine AUC ↑ 17%	No dose adjustment necessary.
Raltegravir (400 mg b.i.d)	Lopinavir AUC ↔ Raltegravir AUC ↓ 30%	No dose adjustment necessary.
Maraviroc (300 mg b.i.d)	Maraviroc AUC ↑ 3.95-fold	In adults, it is recommended that the maraviroc dose be reduced by 50% when co-treating with lopinavir/ritonavir.
Enfuvirtide	Not studied, but no interaction expected.	No dose adjustment necessary.
Atazanavir (300mg q.d.)	Atazanavir AUC unchanged, C_{min} ↑ 45% (compared to atazana-vir/ritonavir 300/100 mg q.d.) Lopinavir AUC unaltered	The benefit of co-administering two protease inhibitors (excepting ritonavir as a pharmacokinetic boosting agent) has not been demonstrated. Furthermore, appropriate doses of HIV protease inhibitors in combination with lopinavir/ritonavir with respect to safety and efficacy have not been established. Therefore, generally co-administration of lopinavir/ritonavir with other PIs is not recommended. If concomitant administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg with PIs is considered necessary, this requires close monitoring.
Darunavir/ritonavir (1200/100 mg q.d.)	Darunavir AUC ↓ 41%, C_{min} ↓ 45% compared to daruna-vir/ritonavir 600/100 mg b.i.d.) Lopinavir AUC unaltered.	
Fosamprenavir/ritonavir (700/100 b.i.d.)	Amprenavir AUC ↓ 63% C_{min} ↓ 65% Lopinavir AUC ↑ 37% C_{min} ↑ 52%	
Indinavir (600 mg q.d.)	Indinavir AUC unaltered, C_{min} ↑ 3.5-fold (compared to indinavir 800 mg t.i.d.). Lopinavir AUC unaltered.	

Nelfinavir (1000 mg b.i.d.)	Lopinavir AUC ↓ 27%, C_{min} ↓ 38% Nelfinavir AUC ↑ 7% C_{min} ↑ 86% (compared to nelfinavir 1250 mg b.i.d.)	
Saquinavir (800 mg b.i.d.)	Saquinavir AUC ↑ 30% (compared to saquinavir/ritonavir 1000/100 mg b.i.d.)	
Tipranavir/ritonavir (500/200 mg b.i.d)	Lopinavir AUC ↓ 47%, C_{min} ↓ 70%	
Anti-Mycobacterial		
Rifampicin (600 mg q.d.; lopinavir/ritonavir SGC 400/100 mg b.i.d.)	Lopinavir AUC ↓ 75%, C_{min} ↓ 99%	The co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and rifampicin is not recommended. Rifabutin is the preferable rifamycin in this situation (see below). In adults, if co-administration is judged unavoidable, a dose adjustment of lopinavir/ritonavir to 400/400 mg twice daily has allowed compensating for the CYP3A4-inducing effect of rifampicin. Also in children, dosing lopinavir and ritonavir at a 1:1 dose ratio has been evaluated. The ritonavir dose should be titrated upward only after rifampicin has been initiated. Patients should be carefully monitored for side effects and therapeutic efficacy.
Rifampicin (600 mg; lopinavir/ritonavir SGC 800/200 b.i.d.)	Lopinavir AUC unchanged, C_{min} ↓ 54% compared to lopinavir/ritonavir 400/100 mg without rifampicin.	
Rifampicin (600 mg q.d.; lopinavir/ritonavir SGC 400/400 mg b.i.d.)	Lopinavir AUC unchanged, C_{min} ↓ 10%, compared to lopinavir/ritonavir 400/100 mg without rifampicin	
Rifabutin (150 mg q.d.)	Rifabutin AUC ↑ 3-fold; 25-O-deacetylrifabutin (active metabolite) AUC ↑ 47.5-fold, compared with rifabutin 300 mg q.d.	In adults rifabutin dose should be reduced by 75%; i.e. to 150 mg every other day, or 150 mg thrice weekly, and safety should be closely monitored. No studies on rifabutin dosing when co-treating with lopinavir/ritonavir in children are available.
Other anti-infectives		
Clarithromycin (500 mg b.i.d., together with ritonavir 200 mg t.i.d.)	Clarithromycin AUC ↑ 77%; 14-OH-clarithromycin (active metabolite)	Clarithromycin doses greater than 1g/day* should not be co-administered with Lopinavir/Ritonavir granules 40 mg/

	AUC ↓ 100%	10 mg. For patients with renal impairment, a clarithromycin dose reduction should be considered (for further details see Summary of Product Characteristics of clarithromycin-containing products).
Erythromycin	No interaction data available. Erythromycin levels may increase	Co-administer with caution and monitor for adverse effects.
Fusidic acid	No interaction data available. Exposure to fusidic acid is expected to increase.	Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and systemically administered fusidic acid should be avoided as this may result in hepatotoxicity.
Vorizonazole (200 mg b.i.d., together with ritonavir 100 mg b.i.d)	Voriconazole AUC ↓ 39%	Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and voriconazole should be avoided due to the risk of therapeutic failure secondary to low voriconazole exposure. If deemed necessary, the therapeutic effect of voriconazole should be carefully monitored, and plasma concentration measured, if feasible.
Itraconazole		Itraconazole exposure may increase. Doses > 200 mg/d are not recommended*
Ketoconazole		Ketoconazole exposure may increase. Doses > 200 mg/d are not recommended*
Fluconazole		No interaction expected.
Sulfamethoxazole/trimethoprim		No interaction expected.
Atovaquone		Atovaquone exposure may decrease. The therapeutic effect should be carefully monitored.
Artemisinin derivatives		No data are available. However artemisinin derivatives are metabolized into active metabolites by CYP3A. The putative interaction effects are unclear. If co-administered, monitor efficacy and safety of artemisinins.
Halofantrine		Halofantrine prolongs the QT interval and is metabolized by CYP3A. Co-administration with Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is contraindicated.
Lumefantrine (480 mg b.i.d.)	Lumefantrine AUC ↑ 193%	Lumefantrine and Lopinavir / Ritonavir Oral Granules 40 mg / 10

		mg should be co-administered with caution.
Quinine (600 mg single dose, ritonavir 200 mg b.i.d)	Quinine AUC and C_{max} ↑ 4-fold (Pharmacokinetic interaction between ritonavir and quinine.	Since quinine may prolong the QT-interval, co-administration should be avoided unless the benefit is considered to outweigh the risk.
Sulfadoxine/pyrimethamine	Not studied, but no interaction expected.	No dose adjustment necessary.
Doxycycline	Not studied, but no interaction expected.	No dose adjustment necessary.
Chloroquine	Chloroquine levels may increase due to CYP3A inhibition.	Co-administer with caution and monitor for chloroquine toxicity.
Mefloquine	Not studied, but no interaction expected.	No dose adjustment necessary.
ANALGESICS		
Buprenorphine (16 mg q.d.)	Buprenorphine and norbuprenorphine AUC ↔	No dose adjustment necessary.
Methadone (5 mg single dose)	Methadone AUC ↓ 53%	Monitor for methadone withdrawal symptoms, and increase methadone dose if necessary.
Morphine	Morphine levels may be decreased due to induction of glucuronidation.	Dose increase may be necessary to maintain therapeutic effect.
Fentanyl, Propoxiphene		Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg co-administration is likely to result in increased plasma concentrations of fentanyl and propoxiphene, and is therefore contraindicated.
Meperidine		The concomitant use of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and meperidine is contraindicated due to increases in concentrations of the metabolite normeperidine which may increase the risk of CNS side effects (e.g. seizures).
ANTIARRHYTHMICS		
Amiodarone Bepridil Quinidine Propafenone		Co-administration with Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is likely to result in increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone and quinidine, and is therefore contraindicated.
Digoxin (0.4 mg SD +	Digoxin AUC: ↑ 22%.	Careful monitoring of digoxin levels

ritonavir 200 mg b.i.d.)	Ritonavir may increase digoxin levels due to modification of P-glycoprotein mediated digoxin efflux.	is recommended when digoxin is administered concomitantly with Lopinavir/Ritonavir granules 40 mg/ 10 mg.
ANTIASTHMATIC		
Theophylline		An increased dose of theophylline may be required due to induction of CYP1A2. Monitor clinical efficacy and theophylline plasma concentration if possible.
ANTICANCER AGENTS		
Ifosfamide Vincristine Vinblastine Etoposide	Serum concentrations of ifosfamide, vincristine, vinblastine and etoposide may be increased due to CYP3A inhibition.	This may results in an increase in the incidence and severity of adverse events. These agents and Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg should be co-administered with caution.
ANTICOAGULANT		
Warfarin		S-warfarin levels may be decreased leading to reduced anticoagulation due to induction of CYP1A2 and CYP2C9 by ritonavir. However, in some patients with aberrant metabolism, warfarin effect may increase dose alterations of warfarin may be necessary, and INR should be monitored closely.
ANTICONVULSANTS		
Carbamazepine	Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and carbamazepine could lead to a two-way interaction, with increased plasma levels of carbamazepine (due to CYP3A inhibition) and decreased levels of lopinavir (due to hepatic enzyme induction).	Co-administration should be avoided. If deemed necessary, monitor clinical efficacy and safety, and plasma concentrations of carbamazepine and lopinavir if possible.
Phenytoin	Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and phenytoin may lead to a two way interaction, with decreased levels of both phenytoin and lopinavir.	Co-administration should be avoided. If deemed necessary, monitor clinical efficacy, and plasma concentrations of phenytoin and lopinavir if possible.
Lamotrigine (100 mg b.i.d)	Lamotrigine	Monitor efficacy and, if possible,

	AUC ↓ 50%	lamotrigine plasma concentration. A dose increase of lamotrigine may be necessary.
Phenobarbital		Co-administration should be avoided, as decreased levels of lopinavir may result due to hepatic enzyme induction by phenobarbital. If co-administration is deemed necessary, monitor efficacy and, if possible, plasma levels of lopinavir.
Valproic acid	Probably no clinically relevant interaction	Monitor efficacy and safety. Probably no dose adjustment will be necessary.
ANTIDEPRESSANTS		
Trazodone (50 mg single dose; ritonavir 200 mg b.i.d.)	Trazodone AUC ↑ 2.4-fold	If trazodone is co-administered with Lopinavir/Ritonavir granules 40 mg/ 10 mg, the combination should be used with caution, intiating trazodone at the lowest dosage and monitoring for clinical response and tolerability.
ANTIPSYCHOTICS		
Pimozide		Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and pimozide is contraindicated, as inhibition of CYP3A may increase the plasma concentration of pimozide.
Clozapine		Co-administer with caution, as Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg may increase plasma levels of clozapine.
ANTIHISTAMINES		
Astemizole Terfenadine		Co-administration with Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is likely to result in increased plasma concentrations of astemizole and terfenadine, and is therefore contraindicated.
CALCIUM CHANNEL BLOCKERS		
Verapamil		Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and verapamil is contraindicated, as increased verapamil plasma levels could cause AV-block.
Diltiazem		Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and diltiazem should not be co-administered, as increased diltiazem plasma levels could cause

		AV-block.
Amlodipine Felodipine Nifedipine		Co-administer with caution. Careful monitoring of adverse effects is recommended when co-administering Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and amlodipine, felodipine, nifedipine or other dihydropyridine calcium channel blockers, since CYP3A blockade by Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg may cause higher plasma levels of these drugs.
HMG-CoA REDUCTASE INHIBITORS		
Simvastatin Lovastatin		Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is contraindicated, as this is likely to lead to increased plasma levels of simvastatin or lovastatin and, thus, to a greater risk of rhabdomyolysis.
Atorvastatin (20 mg q.d.)	Atorvastatin AUC ↑ 5.9-fold	If co-administered, the lowest possible initial dose of atorvastatin should be used, and the patient should be closely monitored for efficacy and safety.
Rosuvastatin (20 mg q.d.)	Rosuvastatin AUC ↑ 2.1-fold	If co-administered, the lowest possible initial dose of rosuvastatin should be used, and the patient should be closely monitored for efficacy and safety.
Pravastatin (20 mg q.d.)	Pravastatin AUC ↑ 33%	No dose adjustment necessary.
Fluvastatin	No clinically relevant interaction expected	No dose adjustment necessary.
IMMUNOSUPPRESSANTS		
Cyclosporine A	Following initiation of ritonavir-boosted PI treatment, a dose reduction of cyclosporine A to 5-20% of prior dose was needed to maintain cyclosporine A levels within therapeutic range.	Co-administer only, if therapeutic drug monitoring of cyclosporine is available. Reduce cyclosporine dose and monitor plasma concentrations closely.
Tacrolimus	The tacrolimus dose, needed to maintain therapeutic concentrations, have often been < 2% when co-administered with a	Co-administer only if therapeutic drug monitoring of tacrolimus is available. Reduce tacrolimus dose and monitor plasma concentrations closely.

	boosted PI, compared to when tacrolimus was given without a PI.	
HORMONAL CONTRACEPTIVES		
Ethinylestradiol 0.035 mg Norethindrone 1 mg	Ethinylestradiol AUC ↓ 42% Norethindrone AUC ↓ 17%	Due to reductions in ethinyl oestradiol concentrations, contraceptive efficacy may be impaired. (Additional) barrier or other non-hormonal methods of contraception should be used.
PDE5 INHIBITORS		
Sildenafil (100 mg SD, ritonavir 500 mg b.i.d.)	Sildenafil AUC ↑ 11-fold	Co-administer with caution. Sildenafil doses should not exceed 25 mg in 48 hours.*
Tadalafil (20 mg SD; ritonavir 200 mg b.i.d.)	Tadalafil AUC ↑ 124%	Co-administer with caution. Tadalafil doses should not exceed 10 mg every 72 hours*
Vardenafil (5 mg single dose; ritonavir 600 mg b.i.d)	Vardenafil AUC ↑ 49-fold	Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and vardenafil is contraindicated.
SEDATIVES/HYPNOTICS		
Triazolam (0.125 mg SD; ritonavir 200 mg, 4 doses)	Triazolam AUC ↑ > 20-fold (no steady state)	Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg co-administration is likely to result in increased plasma concentrations of triazolam, and is therefore contraindicated.
Clorazepate Diazepam Estazolam Flurazepam		Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam, through inhibition of CYP3A, and is therefore contraindicated.
Midazolam	Midazolam $AUC_{(oral)}$ ↑ 13-fold $AUC_{(parenteral)}$ ↑ 4-fold	Co-administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and oral midazolam is contraindicated. If Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is co-administered with parenteral midazolam, it should be done in an intensive care unit or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. A reduced dose should be considered, especially if more than a single dose of

		midazolam is administered.
Alprazolam	Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect was observed.	Caution is warranted during the first several days when alprazolam is co-administered with Lopinavir/Ritonavir granules 40 mg/ 10 mg, before induction of alprazolam metabolism develops.
Oxazepam	Due to induction of glucuronidation, oxazepam clearance may be increased.	Monitor oxazepam efficacy and increase dose if necessary.
STEROIDS		
Fluticasone propionate aqueous nasal spray (0.2 mg q.d; ritonavir 100 mg b.i.d.)	Fluticasone AUC ↑ 350-fold	Concomitant administration of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg and fluticasone or other inhaled corticosteroids (e.g. budesonide, mometasone) that are substrates of CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. The use of a corticosteroid which is not a substrate of CYP3A (e.g. beclomethasone) should be preferred.
Prednisolone (20 mg SD; ritonavir 200 mg b.i.d.)	Prednisolone AUC ↑ 30%	Monitor for corticosteroid efficacy and side effects and dose adjust if necessary.
MISCELLANEOUS		
Alfuzosin	Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is likely to increase plasma concentrations of alfuzosin.	The combination should be avoided.
Dihydroergotamine Ergonovine Ergotamine Methylergovine		Co-administration of ergot derivatives and Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is contraindicated, as this is likely to lead to increased plasma levels of the ergot derivatives.
Cisapride		Co-administration of cisapride and Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is contraindicated, as this is likely to lead to increased plasma levels of cisapride.
St John's Wort		Serum levels of lopinavir may decrease due to concomitant use of the herbal preparation St John's Wort. Co-administration is

		contraindicated.

*** These doses refer to treatment in adult patients. The interaction concerns, however, should be considered of relevance also when treating paediatric patients.**

4.6 Pregnancy and lactation

Pregnancy:
As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus. Lopinavir/ritonavir has been evaluated in over 3000 women during pregnancy, including over 1000 during the first trimester.
In post-marketing surveillance through the Antiretroviral Pregnancy Registry, established since January 1989, an increased risk of birth defects exposures with Lopinavir/ritonavir has not been reported among over 1000 women exposed during the first trimester. The prevalence of birth defects after any trimester exposure to lopinavir is comparable to the prevalence observed in the general population. No pattern of birth defects suggestive of a common etiology was seen. Studies in animals have shown reproductive toxicity (see section 5.3). Based on the data mentioned, the malformative risk is unlikely in humans. Lopinavir can be used during pregnancy if clinically needed.

Lactation: Studies in rats revealed that lopinavir is excreted in the milk. It is not known whether this medicinal product is excreted in human milk. 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.

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 the adverse reaction profile of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg 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 lopinavir therapy is diarrhoea and was generally of mild to moderate severity. Also, dyslipidaemia, including hypertriglyceridaemia and hypercholesterolaemia are common, and may require drug treatment or discontinuation of Lopinavir/Ritonavir.

It is important to note that cases of pancreatitis have been reported in patients receiving ritonavir-boosted lopinavir. Furthermore, rare increases in the PR interval have been reported during therapy with ritonavir-boosted lopinavir.

The following adverse reactions of moderate to severe intensity with possible or probable relationship to lopinavir/ritonavir have been reported. The adverse reactions are displayed by system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common (≥ 1/10), common (≥ 1/100 to < 1/10),

uncommon (≥ 1/1000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000).

Undesirable effects in clinical studies in adult patients		
System Organ Class	**Frequency**	**Adverse Reaction**
Investigations	Very common (Grade 3 or 4)	Blood triglycerides increased, blood cholesterol increased, glutamyltransferase increased
	Common (Grade 3 or 4)	Blood glucose increased, blood amylase increased, aspartate aminotransferase increased, alanine aminotransferase increased, liver function tests abnormal
	Uncommon	Glucose tolerance decreased, blood bilirubin increased, creatinine renal clearance decreased, lipase increased, weight increased, weight decreased, hormone level abnormal, laboratory test abnormal
	Rare	Blood alkaline phosphatase increased
Cardiac disorders	Uncommon	Myocardial infarction[1], palpitations
	Rare	Atrioventricular block
Blood and lymphatic system disorders	Uncommon	Anaemia, leucopenia, lymphadenopathy
	Rare	Splenomegaly
Nervous system disorders	Common	Headache, paraesthesia
	Uncommon	Extrapyramidal disorder, migraine, facial palsy, encephalopathy, dizziness, amnesia, coordination abnormal, hypertonia, neuropathy, neuropathy peripheral, somnolence, tremor, ageusia, dysgeusia, dyskinesia
Eye disorders	Uncommon	Visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
	Rare	Vertigo, hyperacusis
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary oedema, dyspnoea, cough
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Nausea, vomiting, abdominal pain, abnormal faeces, dyspepsia, flatulence, gastrointestinal disorder
	Uncommon	Haemorrhagic colitis, pancreatitis[2], enterocolitis, oesophagitis, constipation, faecal incontinence, abdominal distension, gastrooesophageal reflux disease, dry mouth, dysphagia, eructation, gastritis, mouth ulcerations, stomatitis, periodontitis
	Rare	Haemorrhoids

Renal and urinary disorders	Uncommon	Nephrolithiasis, nephritis, albuminuria, hypercalcinuria, urine abnormality

Skin and subcutaneous tissue disorders	Common	Rash, lipodystrophy acquired, acne
	Uncommon	Alopecia, eczema, dermatitis exfoliative, rash maculopapular, dermatitis allergic, dry skin, nail disorder, pruritis, seborrhoea, skin discoloration, skin ulcer, hyperhidrosis, skin striae
	Rare	Idiopathic capillaritis
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, osteoarthritis, myalgia, back pain, arthropathy
Endocrine disorders	Uncommon	Cushing syndrome, hypothyroidism, hypogonadism male
Metabolism and nutrition disorders	Uncommon	Diabetes mellitus, dehydration, lactic acidosis, oedema, increased appetite, obesity, anorexia, hyperglycaemia, hypocholesteraemia, lipomatosis, hyperuricaemia, hypovitaminosis
	Rare	Hypophosphataemia, decreased appetite
Infections and infestations	Uncommon	Gastroenteritis, otitis media, bronchitis, sinusitis, sialadenitis, furunculosis, bacterial infection, viral infection, pharyngitis, influenza, rhinitis
	Rare	Cellulitis, folliculitis, perineal abscess
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	Benign neoplasm of skin
Vascular disorders	Uncommon	Hypertension, thrombophlebitis, deep vein thrombosis, vasculitis, varicose vein, angiopathy
General disorders and administration site conditions	Common	Asthenia, pain
	Uncommon	Chest pain, chest pain substernal, chills, pyrexia, malaise, oedema peripheral, face oedema, drug interaction, cyst
Immune system disorders	Uncommon	Drug hypersensitivity
	Rare	Immune reconstitution syndrome
Hepatobiliary disorders	Uncommon	Hepatitis, cholecystitis, hepatic steatosis, hepatomegaly, liver tenderness
Reproductive system and breast disorders	Uncommon	Amenorrhoea, menorrhagia, ejaculation disorder, erectile dysfunction, breast enlargement, gynaecomastia
Psychiatric disorders	Common	Insomnia
	Uncommon	Agitation, anxiety, confusional state, depression, affect lability, abnormal dreams, decreased libido, nervousness, abnormal thinking

1 This event had a fatal outcome.

2 See: pancreatitis and lipids

Paediatric patients

In children 14 days of age and older, the nature of the safety profile is similar to that seen in adults.

Undesirable effects in clinical studies in paediatric patients		
Infections and infestations	Common	Viral infection
Nervous system disorders	Common	Taste perversion
Gastrointestinal disorders	Common	Constipation, vomiting, pancreatitis*
Hepatobiliary disorders	Common	Hepatomegaly
Skin and subcutaneous tissue disorders	Common	Rash, dry skin
General disorders and administration site conditions	Common	Fever
Investigations	Common (Grade 3 or 4)	Increased activated partial thromboplastin time, decreased haemoglobin, decreased platelets, increased sodium, increased potassium, increased calcium, increased bilirubin, increased ALT, increased AST, increased total cholesterol, increased amylase, increased uric acid, decreased sodium, decreased potassium, decreased calcium, decreased neutrophils

*see: pancreatitis and lipids

Post marketing experience

Hepatitis, and rarely jaundice, have been reported in patients on lopinavir/ritonavir therapy in the presence or absence of identifiable risk factors for hepatitis.
Stevens-Johnson syndrome and erythema multiforme have been reported.
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. The frequency of this is unknown.

4.9 Overdose

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

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

There is no specific antidote for overdose with Lopinavir/Ritonavir Granules 40 mg/ 10 mg. Treatment of overdose with Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is to consist of general supportive measures including monitoring of vital signs and observation of the

clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since lopinavir and ritonavir are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: protease inhibitor, ATC code: J05AR10
Namibia Pharmacological Classification: 20.2.8 – Antiviral agents

Mechanism of action: Lopinavir provides the antiviral activity of Lopinavir/Ritonavir granules 40 mg/ 10 mg. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Antiviral activity in vitro: The *in vitro* antiviral activity of lopinavir against laboratory and clinical HIV strains was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean IC_{50} of lopinavir against five different HIV-1 laboratory strains was 19 nM. In the absence and presence of 50% human serum, the mean IC_{50} of lopinavir agaist 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 seen 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 three 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, when 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} againt 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 pretreated 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 (please refer to the SPCs of these darunavir or tipranavir-containing products for more 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 NRTI 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 is varying depending on the activity of the background regimen and the sensitivity of the virus to lopinavir (see above).

Paediatric Use
M98-940 is an open-label study of a liquid formulation of lopinavir/ritonavir in 100 antiretroviral naïve (44%) and experienced (56%) paediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomised to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naïve patients also received nucleoside reverse transcriptase inhibitors. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors. Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after 3 weeks of therapy in each patient. Subsequently, all patients were continued on the 300/75 mg per m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14 patients less than

2 years old and 6 patients one year or less. Mean baseline CD4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 log_{10} copies/ml. Through 48 weeks of therapy, the proportion of patients with HIV RNA < 400 copies/ml was 84% for antiretroviral naïve patients and 75% for antiretroviral experienced patients and the mean increases from baseline in CD4 cell count were 404 cells/ mm^3 and 284 cells/ mm^3 respectively.

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 observed with recommended once daily or twice daily LPV/r doses at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving lopinavir/ritonavir in the same study on Day 3. The mean changes from baseline in PR interval ranged from 11.6 ms to 24.4 ms in the 12 hour interval post dose. Maximum PR interval was 286 msec and no second or third degree heart block was observed.

5.2 Pharmacokinetic properties

Lopinavir is almost completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of ritonavir-boosted lopinavir 400/100 mg twice daily yields mean steady-state lopinavir plasma concentrations 15 to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg twice daily. The *in vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg is due to lopinavir.

Absorption

Following single dose of administration of two sachets of Lopinavir/Ritonavir Oral Granules 40 mg/10 mg in healthy volunteers, under fed conditions, the mean (±SD) lopinavir Cmax value was 481.615 (± 328.4455) ng/mL and the corresponding value for AUC0-t was 4403.601 (± 3490.8086) ng.hr/mL. The mean (±SD) Lopinavir Tmax value was 5.00 (range: 3.50 - 12.00) hours. The mean (±SD) Ritonavir Cmax value was 31.444 (± 16.3028) ng/mL and the corresponding value for AUC0-t was 265.845 (± 152.8080) ng.hr/mL. The mean (±SD) Ritonavir Tmax value was 4.50 (range: 4.50 - 6.50) hours.

Distribution

At steady state, lopinavir is approximately 98 − 99% bound to serum proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. Lopinavir has been detected in cerebrospinal fluid at concentrations exceeding the IC_{50} of wild-type virus and has been shown 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 with time 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 l/h.

Special populations

Paediatrics: There are limited pharmacokinetic data in children below 2 years of age. The pharmacokinetics of a lopinavir/ritonavir oral solution 300/75 mg/m^2 twice daily and 230/57.5 mg/m^2 twice daily have been studied in a total of 53 paediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen without nevirapine. Lopinavir/ritonavir given once daily has not been evaluated in paediatric patients.

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 have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic insufficiency: The steady state pharmacokinetic parameters of lopinavir in HIV-infected patients with mild-to-moderate hepatic impairment were compared with those of HIV-infected patients with normal hepatic function in a multiple dose study with lopinavir/ritonavir 400/100 mg twice daily. A limited increase in total lopinavir concentrations of approximately 30% has been observed, 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 thyorxine levels led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs. Enlarged spleens with histiocytosis were seen in rats but not other species. Serum Cholesterol was elevated in rodents but not dogs, while triglycerides were elevated only in mice.

During *in vitro* studies, cloned human cardiac potassium channels (hERG) were inhibited by

30% at the highest concentrations of lopinavir/ritonavir tested, corresponding to a lopinavir exposure 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.

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

Long-term carcinogenicity studies of lopinavir/ritonavir in mice revealed a non-genotoxic, mitogenic induction of liver tumours, generally considered to have little relevance to human risk. Carcinogenicity studies in rats revealed no tumourigenic findings. Lopinavir/ritonavir was not found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone, Sorbitan monolaurate, Colloidal Silicon dioxide, Ethyl Cellulose, Mannitol, Acesulfam Potassium, Sodium Stearyl Fumarate, Vanilla flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 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

Available as sachets, comprises of printed triple laminated roll with aluminium foil, soft, dull side PET and bright side laminated to PE film.

6.6 Special precautions for disposal

Discard unused portion in accordance with local requirements.

7. APPLICANT/MANUFACTURER

Marketing Authorization Holder

HEALTHLINE LIMITED

Reference list:

General references:
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