Summary of Product Characteristics
Lopinavir and Ritonavir
Film Coated Tablet

1. Name of The Medicinal Product
LOPIVIA 200/50

2. Qualitative and Quantitative Composition
Each tablet contains: Lopinavir 200 mg Ritonavir 50 mg
For a full list of excipients see section 12.

3. Pharmaceutical Form
Film-coated tablet Yellow coloured, capsule shaped, biconvex, film-coated tablets debossed with "M32" on one side and plain on the other side. No score-line. The tablet should not be divided.

4. Pharmacology
Mechanism of action : Lopinavir, an inhibitor of the HIV-1 and HIV-2 proteases, prevents cleavage of the *gag-pol* polyprotein, resulting in the production of immature, non infectious virus.
Genotypic correlates of reduced virologic response in antiretroviral-experienced patients initiating a lopinavir/ritonavir-based combination regimen.

Special population
Gender, race and age
Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No important pharmacokinetic differences due to race have been identified.

Pharm- Renal Impairment
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.

Pharm-Hepatic Impairment
Lopinavir is principally metabolized and eliminated by the liver. Multiple dosing of Lopinavir/Ritonavir 400/100 mg twice daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment resulted increase in Lopinavir AUC and increase in C_{max} compared to HIV-infected subjects with normal hepatic function.
Additionally, the plasma protein binding of Lopinavir was lower in both mild and moderate hepatic impairment compared to controls Lopinavir/Ritonavir has not been studied in patients with severe hepatic impairment (see PRECAUTIONS).

5. Indications
Lopinavir/Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-infection as a second line treatment. There are no results from the effect of Lopinavir/Ritonavir on progression of HIV.
Once daily administration of Lopinavir/Ritonavir has not been studied in therapy-experienced patients.

6. Contraindications
- ✓ Lopinavir/Ritonavir is contraindicated in patients with known hypersensitivity to Lopinavir, Ritonavir, or any excipients.
- ✓ Lopinavir/Ritonavir should not be co-administered concurrently with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 1.

Table 1. Drugs which should not be co-administered with Lopinavir/Ritonavir

Drug class	Drug within class not to be co-administered
Alpha I -adrenoreceptor antagonist	Alfuzosin HCl
Antianginal	Ranolazine
Antiarrithmic	Dronadrone
Fusidic acid	Fusidic acid
Antigout	Colcihine in patient with renal and/or hepatic impairment
Antihistamines	Astemizole, Terfenadine
Antipsychotic	Blonanserin, Lurasidone, Pimozide
Benzodiazepines	Midazolam, Triazolam
Ergot derivatives	Ergotamine, Dihydroergotamine, Ergonovine, Methylergonovine
GI motility agent	Cisapride
Herbal product	St. John's Wort (*Hypericum perforatum*)
HMG-CoA Reductase Inhibitors	Lovastatin-Simvastatin
Long acting beta - adrenoceptor agonist	Salmeterol
Neuroleptics	Pimozide
PDE5 enzyme inhibitor	Sildenafil* (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH)
*see WARNINGS AND PRECAUTIONS and DRUGS INTERACTIONS for co-administration of Sildenafil patients with erectile dysfunction.	

- ✓ Patients with severe hepatic insufficiency.

7. Dosage and Administrations
Adults
Lopinavir/Ritonavir tablets should be swallowed whole and not chewed, broken or crushed. The recommended oral dose of Lopinavir/Ritonavir is as follows :
a. Therapy-naive patients
Lopinavir/Ritonavir tablets 400/100 mg (given as two, 200/50 mg tablets) twice-daily with or without food.
Lopinavir/Ritonavir tablets 800/200 mg (given as two, 200/50 mg tablets) once-daily taken with or without food.
b. Therapy-experienced patients
Lopinavir/Ritonavir tablets 400/100 mg (given as two, 200/50 mg tablets) twice-daily taken with or without food.
Once daily administration of Lopinavir/Ritonavir has not been studied in therapy-experienced patients.

Concomitant therapy :
a. Omeprazole and Ranitidine
Lopinavir/Ritonavir tablets can be used in combination with acid reducing agents (Omeprazole and Ranitidine) with no dose adjustment (see Table 1).
b. Efavirenz, Nevirapine, Amprenavir, or Nelfinavir
Lopinavir/Ritonavir 400/100 mg tablets can be used twice daily in combination with these drugs with no dose adjustment (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).
Lopinavir/Ritonavir should not be administered as a once-daily regimen in combination with Efavirenz, Nevirapine, Amprenavir or Nelfinavir.

c. Concomitant therapy : Efavirenz, Nevirapine, Amprenavir or Nelfinavir. A dose increase of Lopinavir/Ritonavir to 533/133 mg twice-daily taken with food is recommended when used in combination with Efavirenz, Nevirapine, Amprenavir or Nelfinavir.

Pediatric
Lopinavir/Ritonavir should not be administered once daily in pediatric patients. The adult dose of Lopinavir/Ritonavir tablets (400/100 mg BID) without concomitant efavirenz, nevirapine, nelfinavir or amprenavir may be used in children weighing 35 kg or greater or with a Body Surface Area (BSA) of 1.4 m^2 or greater. For children weighing less than 35 kg or with a BSA between 0.6 to 1.4 m^2 and able to swallow tablets, please refer to the dosing table below.

The following table contains dosing guidelines for lopinavir/ritonavir 100/25 mg tablets based on BSA :

Pediatric Dosing Guidelines Based on BSA Without Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Body Surface Area (m^2)	Recommende Number of 100/25 mg Tablets Twice-Daily
≥ 0.6 - < 0.9	2 tablets (200/50 mg)
> 0.9 - < 1.4	3 tablets (300/75 mg)
≥ 1.4	4 tablets (400/100 mg)

Body surface area can be calculated with the following equation:
*BSA (m^2) = SQR RT [Height (cm) x Weight (kg)] / 3600

Concomitant therapy : Efavirenz, Nevirapine, Nelfinavir, or Amprenavir
The following table contains dosing guidelines for lopinavir/ritonavir 100/25 mg tablets based on BSA when used in combination with Efavirenz, Nevirapine, Nelfinavir or Amprenavir in children:

Pediatric Dosing Guidelines Based on BSA With Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Body Surface Area (m^2)	Recommende Number of 100/25 mg Tablets Twice-Daily
≥ 0.6 - < 0.8	2 tablets (200/50 mg)
> 0.8 - < 1.2	3 tablets (300/75 mg)
≥ 1.2 to <1.7	4 tablets (400/100 mg)
≥ 1.7	5 tablets (500/125 mg)

The following table contains dosing guidelines for Lopinavir/Ritonavir 100/25 mg tablets based on body weight :

Pediatric Dosing Guidelines Based on Weight Without Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Weight (kg)	Number of 100/25 mg Tablets twice-daily
15 to 25 kg	2
>25-35	3
> 35	4 #

Alternatively, two 200/50 mg tablet may be used for this dose in patients who can swallow the larger tablet. Concomitant Therapy : Efavirenz, Nevirapine, Nelfinavir or Amprenavir

Concomitant therapy : Efavirenz, Nevirapine, Nelfinavir, or Amprenavir
The following table contains dosing guidelines for Lopinavir/ Ritonavir 100/25 mg tablets based on body weight when used in combination with Efavirenz, Nevirapine, Nelfinavir or Amprenavir in children:

Pediatric Dosing Guidelines Based on Weight With Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Weight (kg)	Number of 100/25 mg Tablets twice-daily
15 to 25 kg	2
>25-35	3
> 35	4 #
> 45 kg	5
# Alternatively, two 200/50 mg tablet may be used for this dose in those patients who can swallow the larger tablet	

8. Warning and Precautions
- ✓ Drug interactions : Lopinavir/Ritonavir is an inhibitor of the P450 isoform CYP3A. Coadministration of Lopinavir/Ritonavir and drugs primarily metabolized by CYP3A or may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects. (see CONTRAINDICATIONS, DRUG INTERACTIONS).
- ✓ Antigout agents : Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like Ritonavir (see CONTRAINDICATIONS and DRUG INTERACTIONS).
- ✓ Anti-mycobacterial : Standard dose Lopinavir/Ritonavir should not be coadministered with Rifampin because large decrease in Lopinavir concentrations may significantly decrease the therapeutic effect (see DRUG INTERACTIONS).
- ✓ Antipsychotics : Caution should be exercised when Lopinavir/Ritonavir is co-administered with Quetiapine. Due to CYP3A inhibition by Lopinavir/Ritonavir, concentrations of Quetiapine are expected to increase, which may lead to Quetiapine-related toxicities (see DRUG INTERACTIONS).
- ✓ Corticosteroids : Concomitant use of Lopinavir/Ritonavir and Fluticasone or other glucocorticoids that are metabolised by CYP3A4, such as Budesonide, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.
- ✓ Concomitant use of Lopinavir/Ritonavir and fluticasone propionate can significantly increase Fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when Lopinavir/Ritonavir has been co-administered with inhaled or intranasally administered Fluticasone propionate or Budesonide (see DRUG INTERACTIONS).
- ✓ PDE5 inhibitors : Co-administration of Lopinavir/Ritonavir with Avanafil is not recommended. Particular caution should be used when prescribing Sildenafil, Tadalafil or Vardenafil for the treatment of erectile dysfunction in patients receiving Lopinavir/Ritonavir. Coadministration of Lopinavir/Ritonavir with these drugs is expected to substantially increase their concentrations and may result in increased associated adverse events such as hypotension, and prolonged erection. Concomitant use of Sildenafil with Lopinavir/Ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients (see CONTRAINDICATIONS and DRUG INTERACTIONS).
- ✓ Herbal products : Patients on Lopinavir/Ritonavir should not use products containing St. John's Wort (*Hypericum perforatum*) because coadministration may be expected to reduce plasma concentrations of protease inhibitors. This may result in loss of therapeutic effect and development of resistance to Lopinavir or to the therapeutic class of protease inhibitors (see CONTRAINDICATIONS and DRUG INTERACTIONS).
- ✓ HMG-CoA reductase inhibitors : Concomitant use of Lopinavir/Ritonavir with Lovastatin or Simvastatin is contraindicated. Caution should be exercised if HIV protease inhibitors, including Lopinavir/Ritonavir, are used concurently with Rosuvastatin or with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (e.g., Atorvastatin), as this may increase the potential for serious reactions such as myopathy, icluding rhabdomyolysis (see DRUG INTERACTIONS).
- ✓ Tipranavir : The concomitant administration of Lopinavir/Ritonavir and Tipranavir with low dose Ritonavir is therefore not recommended.
- ✓ Diabetes mellitus/hyperglycemia : New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occured. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. Consideration should be given the monitoring of blood glucose.
- ✓ Pancreatitis : Pancreatitis has been observed in patients receiving Lopinavir/Ritonavir therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been obeserved. Although a causal relationship to Lopinavir/Ritonavir has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see WARNINGS AND PRECAUTIONS). Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during Lopinavir/Ritonavir therapy.
- ✓ Hepatic impairment : Lopinavir/Ritonavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function. Lopinavir/Ritonavir has not been studied in patients with severe hepatic impairment. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations. There have been reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with Lopinavir/Ritonavir therapy has not been established. Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-I mono-infected and uninfected patients as early as 7 days after the initiation of Lopinavir/Ritonavir in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with Lopinavir/Ritonavir therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of Lopinavir/Ritonavir treatment.
- ✓ Resistance/cross-resistance : Various degrees of cross-resistance among protease inhibitors have been observed. The effect of Lopinavir/Ritonavir therapy on the efficacy of subsequently administered protease inhibitors is under investigation.
- ✓ Hemophilia : There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. Neither a causal relationship or a mechanism of action between protease inhibitor therapy and these events has been established.
- ✓ PR Interval Prolongation : Lopinavir/Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Reports of second or third degree atrioventricular block in patients with underlying structural heart disease and preexisting conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as Verapamil or Atazanavir) have been reported in patients receiving Lopinavir/Ritonavir. Lopinavir/Ritonavir should be used with caution in such patients.
- ✓ Fat redistribution : Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.
- ✓ Lipid elevations : Treatment with Lopinavir/Ritonavir has resulted in increase in the concentration of total cholesterol and tryglycerides. Triglyceride and cholesterol testing should be performed prior to initiating Lopinavir/Ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as appropriate. See WARNINGS AND PRECAUTIONS : HMG-CoA Reductase Inhibitors for additional information on potential drug interactions with Lopinavir/Ritonavir and HMG CoA reductase inhibitors.
- ✓ Immune reconstitution syndrome : Immune reconstitution syndrome has been reported in HIV- infected patients treated with combination antiretroviral therapy, including Lopinavir/Ritonavir. During the initial phase of combination antiretroviral treatment when the immune system responds, patients may develop an inflammatory response to asymptomatic or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci pneumonia*, or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.
- ✓ Osteonecrosis : Although the etiology is considered to multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long- term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.
- ✓ Geriatric Use : In general, appropriate caution should be exercised in the administration and monitoring of Lopinavir/Ritonavir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
- ✓ Pediatric Use : The safety and pharmacokinetic profiles of Lopinavir/Ritonavir in pediatric patients below the age of six months have not been established. Lopinavir/Ritonavir once daily has not been evaluated in pediatric patients.

9. Drug Interactions
- ✓ Lopinavir/Ritonavir is an inhibitor of CYP3A (cytochrome P450 3A) both in vitro and in vivo. Coadministration of Lopinavir/Ritonavir and drugs primarily metabolized by CYP3A (e.g., Dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and Sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see WARNINGS AND PRECAUTIONS). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when coadministered with Lopinavir/Ritonavir. Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events.

Anti-HIV Agents
- ✓ Nucleoside Reverse Transcriptase Inhibitors (NRTIs) :

a. Stavudine and Lamivudine : No change in the pharmacokinetics of Lopinavir was observed when Lopinavir/Ritonavir was given alone or in combination with Stavudine and Lamivudine.
b. Didanosine : It is recommended that Didanosine be administered on an empty stomach; therefore, Didanosine may be coadministered with Lopinavir/Ritonavir tablets without food.
c. Zidovudine and Abacavir : Lopinavir/Ritonavir induces glucuronidation, therefore Lopinavir/Ritonavir has the potential to reduce Zidovudine and Abacavir plasma concentrations. The significance of this potential interaction is unknown.

d. Tenofovir : Lopinavir/Ritonavir increases Tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving Lopinavir/Ritonavir and Tenofovir should be monitored for Tenofovir-associated adverse events.

e. All : Increased CPK, myalgia, myositis, and rarely, rhabdomyolysis have been reported with PIs, particularly in combination with NRTIs.

✓ Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTs) :

a. Nevirapine : No change in the pharmacokinetics of Lopinavir was apparent in healthy adult subjects during Nevirapine and Lopinavir/Ritonavir co-administration. In HIV-positive pediatric subjects revealed a decrease in Lopinavir concentrations during Nevirapine coadministration. The effect of Nevirapine in HIV-positive adults is expected to be similar to that in pediatric subjects and Lopinavir concentrations may be decreased. The significance of the pharmacokinetic interaction is unknown. For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward Lopinavir, dosage increase of Lopinavir/Ritonavir tablets to 500/125 mg BID should be considered when co-administered with Nevirapine. Lopinavir/Ritonavir should not be administered once daily in combination with Nevirapine.

b. Efavirenz : For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward Lopinavir, dosage increase of Lopinavir/Ritonavir tablets to 500/125 mg BID should be considered when co-administered with Efavirenz.Increasing the dose of Lopinavir/Ritonavir tablets to 600/150 (three (3) tablets) BID coadministered with Efavirenz significantly increased the Lopinavir plasma concentrations and Ritonavir concentrations compared to Lopinavir/Ritonavir tablets 400/100 mg BID without Efavirenz. NOTE : Efavirenz and Nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with Lopinavir/Ritonavir. Lopinavir/Ritonavir should not be administered once daily in combination with Efavirenz.

c. Delavirdine : Delavirdine has the potential to increase concentrations of Lopinavir.

d. Rilpivirine : Concomitant use of Lopinavir/Ritonavir with Rilpivirine causes an increase in the plasma concentrations of Rilpivirine, but no dose adjustment is required. Refer to the Rilpivirine prescribing information.

e. Etravirine : Concomitant use of Lopinavir/Ritonavir with Etravirine causes a decrease in the plasma concentrations of Etravirine, but no dose adjustment is required. Refer to the etravirine prescribing information.

✓ Protease Inhibitors (PIs) :

a. Amprenavir : Lopinavir/Ritonavir is expected to increase concentrations of Amprenavir (Amprenavir 750 mg BID plus Lopinavir/Ritonavir produces increased AUC, similar C_{max}, increased C_{min}, relative to Amprenavir 1200 mg BID). Co-administration of Lopinavir/Ritonavir and Amprenavir result in decreased concentrations of Lopinavir. The dose of Lopinavir/Ritonavir may need to be increased during co-administration of Amprenavir, particularly in patients with extensive protease inhibitor experience or reduced viral susceptibility to Lopinavir (see DOSAGE AND ADMINISTRATIONS). Lopinavir/Ritonavir should not be administered once daily in combination with Amprenavir.

b. Fosamprenavir : Coadministration of Lopinavir/Ritonavir with Fosamprenavir lowers Amprenavir and Lopinavir concentrations. Appropriate doses of the combination of Fosamprenavir and Lopinavir/Ritonavir with respect to safety and efficacy have not been established.

c. Indinavir : Lopinavir/Ritonavir is expected to increase concentrations of Indinavir (Indinavir 600 mg BID plus Lopinavir/Ritonavir produces similar AUC, decreased C_{max}, increased C_{min} relative to Indinavir 800 mg TID). The dose of Indinavir may need to be decreased during co-administration of Lopinavir/Ritonavir 400/100 mg BID. Lopinavir/Ritonavir once daily has not been studied in combination with Indinavir.

d. Nelfinavir : Lopinavir/Ritonavir is expected to increase concentrations of Nelfinavir and increased M8 metabolite of Nelfinavir (Nelfinavir 1000 mg BID plus Lopinavir/Ritonavir produces similar AUC, similar C_{max}, increased C_{min} relative to Nelfinavir 1250 mg BID). Co-administration of Lopinavir/Ritonavir and Nelfinavir result in decreased concentrations of Lopinavir. Lopinavir/Ritonavir should not be administered once daily in combination with Nelfinavir.

e. Ritonavir : When Lopinavir/Ritonavir was coadministered with an additional 100 mg Ritonavir twice daily, Lopinavir AUC increased and C_{min} increased as compared to Lopinavir/Ritonavir 400/100 mg (three (3) soft gel capsules) twice daily.

f. Saquinavir : Lopinavir/Ritonavir is expected to increase concentrations of Saquinavir (Saquinavir 800 mg BID plus Lopinavir/Ritonavir produces increased AUC, increased C_{max}, increased C_{min} relative to Saquinavir 1200 mg TID). The dose of Saquinavir may need to be decreased when coadministered with Lopinavir/Ritonavir 400/100 mg BID. Lopinavir/Ritonavir once daily has not been studied in combination with Saquinavir.

✓ HCV- Protease Inhibitors

a. Telaprevir : Concomitant administration of telaprevir and lopinavir/ritonavir resulted in reduced telaprevir steady-state exposure, while the lopinavir steady-state exposure was not affected.

b. Boceprevir : Concomitant administration of Boceprevir and Lopinavir/Ritonavir resulted in reduced Boceprevir and Lopinavir steady-state exposure. It is not recommended to co-administer Lopinavir/Ritonavir and Boceprevir.

✓ HIV CCR1 – antagonist

a. Maraviroc : Concurrent administration of Maraviroc with Lopinavir/Ritonavir will increase plasma levels of Maraviroc. The dose of Maraviroc should be decreased during co-administration with Lopinavir/Ritonavir 400/100 mg BID. For further details, see complete prescribing information for Maraviroc.

✓ Other drugs :

a. Analgesic Fentanyl : Lopinavir/Ritonavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of Fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when Fentanyl is concomitantly administered with Lopinavir/Ritonavir.

b. Antiarrhythmics (Amiodarone, Bepridil, Systemic Lidocaine and Quinidine) : Concentrations may be increased when coadministered with Lopinavir/Ritonavir. Caution is warranted and therapeutic concentration monitoring is recommended when available.

c. Digoxin : A literature report has shown that coadministration of Ritonavir (300 mg every 12 hours) and Digoxin resulted in significantly increased Digoxin levels. Caution should be exercised when coadministering Lopinavir/Ritonavir with Digoxin, with appropriate monitoring of serum Digoxin levels.

d. Anticancer Agents (e.g. Dasatinib, Nilotinib, Vincristine, Vinblastine) : May have their serum concentrations increased when co-administered with Lopinavir/Ritonavir resulting in the potential for increased adverse events usually associated with these anticancer agents. For Nilotinib and Dasatinib, refer to their prescribing information for dosing instructions.

e. Anticoagulant : Warfarin concentrations may be affected when co-administered with Lopinavir/Ritonavir. It is recommended that INR (International Normalized Ratio) be monitored. Rivaroxaban : Co-adminstration of Rivaroxaban and Lopinavir/Ritonavir may increase Rivaroxaban exposure which may increase the risk of bleeding.

f. Anticonvulsants (Phenobarbital, Phenytoin, Carbamazepine) : These drugs are known to induced CYP3A4 and may decrease Lopinavir concentrations. Lopinavir/Ritonavir should not be administered once daily in combination with Phenobarbital, Phenytoin, or Carbamazepine. In addition, co-administration of Phenytoin and Lopinavir/Ritonavir resulted in moderate decreases in steady-state Phenytoin concentrations. Phenytoin levels should be monitored when co-administering with Ritonavir/Ritonavir. Lamotrigine and Valproate : Co-administration of Lopinavir/Ritonavir and either of these drugs was associated with reduction in exposure of the anticonvulsant; reduction in Lamotrigine exposure has been reported. Use with caution. A dose increase of the anticonvulsant may be needed when co-administered with Lopinavir/Ritonavir and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments.

g. Antidepressants :
Bupropion : Concurrent administration of Bupropion with Lopinavir/Ritonavir will decrease plasma levels of both Bupropion and its active metabolite (Hydroxybupropion).
Trazodone : Concomitant use of Ritonavir and Trazodone may increase concentrations of Trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed. If Trazodone is used with a CYP3A4 inhibitor such as Lopinavir/Ritonavir, the combination should be used with caution and a lower dose of Trazodone should be considered.

h. Antifungals : Ketoconazole and Itraconazole may have serum concentrations increased by Lopinavir/Ritonavir. High doses of Ketoconazole and Itraconazole (greater than 200 mg/day) are not recommended.
Voriconazole : Co-administration of Lopinavir/Ritonavir and Voriconazole should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of Voriconazole. Concentrations of Colchicine are expected to increase when co-administered with Lopinavir/Ritonavir. Refer to the Colchicine label for prescribing information. Life-threatening and fatal drug interactions have been reported in patients treated with Colchicine ancl Ritonavir (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

I. Anti-infective : Moderate increases Clarithomycin AUC are expected when coadministered with Lopinavir/Ritonavir. For patients with renal or hepatic impairment dose reduction of Clarithomycin should be considered.

j. Anti-mycobacterial : Rifabutin dose reduction of 75% (i.e. 150 mg every other day or three times per week) is recommended when administered with Lopinavir/Ritonavir. Further dose reduction of Rifabutin may be necessary. Due to large decreases in Lopinavir concentrations, Rifampin should not be used in combination with standard dose Lopinavir/Ritonavir (see WARNINGS AND PRECAUTIONS). The use of Rifampin with Lopinavir/Ritonavir, may lead to loss of virologic response and possible resistance to Lopinavir/Ritonavir or to the class of protease inhibitors or other co-administered antiretroviral agents. Co-administration of Rifampicin with 800/200 mg Lopinavir/Ritonavir BID resulted in decreases in Lopinavir and with Lopinavir/Ritonavir 400/400 mg BID resulted in decreases when compared to Lopinavir/Ritonavir 400/100 mg BID dosed in the absence of Rifampicin. ALT and AST elevations have been noted in studies with higher doses of Lopinavir/Ritonavir co-administered with Rifampicin and may be dependent on the sequence of dose administration. If co-administration is being considered, Lopinavir/Ritonavir should be initiated at standard doses for approximatety 10 days prior to addition of Rifampicin. Lopinavir/Ritonavir dose should then be titrated upward. Close monitoring of liver function is indicated.
Bedaquiline : 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 cautions. More frequent electrocardiogram monitoring & monitoring of transaminase is recommended.

k. Antiparasitic : Decreases in the therapeutic concentration of Atovaquone are possible when coadministered with Lopinavir/Ritonavir. Increases in Atovaquone doses may be necessary.

l. Corticosteroids :
Dexamethasone : May incluce CYP3A4 and may decrease Lopinavir concentrations. Inhaled, injectable or intranasal, fluticasone propionate, budesonide, triamcinolone : Concomitant use of Lopinavir/Ritonavir 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. Consider alternatives to Fluticasone propionate, particularly for long- term use.

m. Dihydropyridines Calcium Channel Blockers (Felodipine, Nifedipine, Nicardipine) : May have their serum concentrations increased by Lopinavir/Ritonavir.

n. PDE5 inhibitors :
Avanafil : Co-administration of Lopinavir/Ritonavir with Avanafil is expected to result in large increases in Avanafil exposure is contraindicated. (see WARNINGS AND PRECAUTIONS).
Sildenafil : Use Sildenafil for the treatment of erectile dysfunction with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events (see WARNINGS AND PRECAUTIONS). Concomitant use of Sildenafil with Lopinavir/Ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients (see CONTRAINDICATIONS).
Tadalafil : Use Tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events (see WARNINGS AND PRECAUTIONS). When Tadalafil is administered in patients with pulmonary arterial hypertension who are receiving lopinavir/ritonavir, refer to the tadalafil label for prescribing information.
Vardenafil : Use Vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events (see WARNINGS AND PRECAUTIONS).

o. Herbal products : Patients on Lopinavir/Ritonavir should not use products containing St. John Wort concomitantly, since this combination may be expected to result in reduced plasma concentrations of Lopinavir/Ritonavir. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

p. HMG-CoA reductase inhibitors : HMG Co-A reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as Lovastatin and Simvastatin, are expected to have markedly increase plasma concentration when coadministered with Lopinavir/Ritonavir. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these drugs with Lopinavir/Ritonavir is contraindicated (see CONTRAINDICATIONS). Atorvastatin is less dependent on CYP3A for metabolism. When atorvastatin was given ooncurrently with Lopinavir/Ritonavir, increase in Atorvastatin C_{max} and AUC, was observed. When used with Lopinavir/Ritonavir, the lowest possible doses of Atorvastatin should be administered. Results from a drug interaction study with Lopinavir/Ritonavir and Pravastatin reveal no clinically significant interaction. The metabolism of Pravastatin and Fluvastatin is not dependent on CYP3A4, and interactions are not expected with Lopinavir/Ritonavir. If treatment with a HMG-CoA reductase inhibitor is indicated, Pravastatin or Fluvastatin is recommended (see WARNINGS AND PRECAUTIONS).

q. Atorvastatin is less dependent on CYP3A for metabolism. When used with Lopinavir/Ritonavir, the lowest possible doses of Atorvastatin should be administered. Result from a drug interaction study with Lopinavir/Ritonavir and Pravastatin reveal no significant interaction. The metabolism of Pravastatin and Fluvastatin is not dependent on CYP3A4, and interactions are not expected with Lopinavir/Ritonavir. If treatment with a HMG-CoA reductase inhibitor is indicated, Pravastatin or Fluvastatin is recommended (see WARNINGS AND PRECAUTIONS).

r. Immunosuppressants : Concentrations of these drugs (e.g. Cyclosporin, Tacrolimus and Sirolimus (Rapamycin)) may be increased when coadministered with Lopinavir/Ritonavir. More frequent therapeutic concentration monitoring is recommended until blood levels of these products have stabilized.

s. Methadone : Lopinavir/Ritonavir was demonstrated to lower plasma concentrations of Methadone. Monitoring plasma concentrations of Methadone is recommended.

t. Oral contaceptives or patch contraceptives : Since levels of Ethinyl estradiol may be decreased, alternative or additional contraceptive measures are to be used when Estrogen-based oral contraceptives or patch contraceptives and Lopinavir/Ritonavir are coadministered.

u. Vasodilating agents : Co-administration of Bosentan and Lopinavir/Ritonavir increased steady-state Bosentan maximum concentration (C_{max}) and area-under-curve (AUC). Refer to the Bosentan label for prescribing information.

v. Significant drug interactions are not expected : Drug interaction studies reveal no significant interaction between Desipramine (CYP2D6 probe), Omeprazole or Ranitidine. No significant interaction between Lopinavir/Ritonavir and Raltegravir. Based on known metabolic profiles, significant drug interactions are not expected between Lopinavir/Ritonavir and Fluvastatin, Dapsone, Trimethoprim/Sulfamethoxazole, Azithromycin, or Fluconazole in patients with normal renal and hepatic function.

✓ Pregnancy : As a general rule, when deciding to use antiretroviral agents for treatment of HIV in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn. There are no adequate and well controlled studies of Aluvia in pregnant women. The prevalence of birth defects after any trimester exposures to Lopinavir is comparable to the prevalence observed in the general population. No pattern of birth defects suggestive of a common etiology was seen.

✓ Lactation : It is not known whether lopinavir is secreted in human milk. As a general rule, it is recommended that mothers iniected by HIV do not breast-feed their babies under any circumtances, in order to avoid transmission of HIV.

✓ Fertility : No human data on the effect of Lopinavir/Ritonavir on fertility are available.

10. Adverse Drug Reactions

Adults

Treatment-emergent adverse reactions

Commonly reported adverse reactions to lopinavir/ritonavir included diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. Diarrhea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridemia and hypercholesterolemia may occur later.

Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in Adults

✓ Blood and lymphatic system disorders : Anemia, leukopenia, lymphadenopathy

✓ Cardiac disorders : Astherosclerosis such as myocardial infarction, atrioventricular block, Tricuspid valve incompetence

✓ Ear and labyrinth disorders : Vertigo, tinnitus

✓ Endocrine disorders : Hypogonadium

✓ Eye disorders : Visual impairment

✓ Gastrointestinal disorders : Diarrhea, nausea, vomiting, abdominal pain (upper and lower), gastroeneteritis and colitis, dyspepsia, pancreatitis, gastroesophageal reflux disease (GERD), hemorrhoids, flatulence, abdominal distention, constipation, stomatitis and oral ulcer, duodenitis and gastritis, gastrointestinal hemonhage including rectal haemorrhage, dry mouth, gastrointestinal ulcer, fecal incontinence

✓ General disorders and administration site conditions : Fatigue including asthenia

✓ Hepatobiliary disorders : Hepatitis including AST, ALT and GGT increases, hepatomegaly, cholangitis, hepatic steatosis

✓ Immune system disorders : Hypersensitivity including urticaria and angioedema, immune reconstitution syndrome

✓ Infections and infestations : Upper respiratory tract infection, lower respiratory tract infection, skin infections including cellulitis, folliculitis, and furuncle

✓ Metabolism and nutrition disorders : Hypercholesterolemia, hypertriglyceridemia, weight decreased, decreased appetite, blood glucose disorders including diabetes mellitus, weight increased, lactic acidosis, increased appetite

✓ Musculoskeletal and connective tissue disorders : Musculoskeletal pain including arthralgia and back pain, myalgia, music disorders such as weakness and spasm, rabdomyolysis, osteonecrosis

✓ Nervous system disorders : Headache including migtaine, insomnia, neuropathy and peripheral neuropathy, dizziness, ageusia, convulsion, tremor, cerebral vascular event

✓ Psychiatric disorders : Anxiety, abnormal dreams, libido decreased

✓ Renal and urinary disorders : Renal failure, hematuria, nephritis

✓ Reproductive system and breast disorders : Erectile dysfunction, menstrual disorders – amenorrhea, menorrhagia

✓ Skin and subcutaneous tissue disorders : Rash including maculopapular rash, lipodystrophy acquired including facial wasting, dermatitis/rash including eczema and seborrheic dermatitis, night sweats, pruritus, alopecia, capillaritis and vasculitis

✓ Vascular disorders : Hypertension, deep vein thrombosis

Pediatric

Treatment-emergent adverse reactions

Dysgeusia, vomiting, and diarrhea were the most commonly reported drug related adverse events of any severity in pediatric patients treated with combination therapy including Lopinavir/Ritonavir. Children experienced moderate or severe adverse events at least possibly related to lopinavir/ritonavir. Rash was the only drug-related clinical adverse event of moderate to severe intensity observed.

11. Overdosage

Human experience of acute overdosage with Lopinavir/Ritonavir is limited. Treatment of overdose with Lopinavir/Ritonavir 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 Lopinavir/Ritonavir. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of active charcoal may also be used to aid in removal of unabsorbed drug. Since Lopinavir/Ritonavir is highly protein bound, dialysis is unlikely to beneficial in significant removal of the drug.

12. Pharmaceutical Particulars

List of Excipients

Core tablet : Copovidone, sorbitan monolaurate, colloidal silicon dioxide, anhydrous dibasic calcium phosphate, isopropyl alcohol, methylene chloride, purified water, and sodium stearyl fumarate.

Film coat : Polyvinyl alcohol-part hydrolysed, titanium dioxide, polyethylene glycol, talc and iron oxide yellow.

Shelf life

24 months

Special precautions for storage

Store below 30°C and protected from light.

Nature and contents of container

Heavy weight HDPE bottle with polypropylene child-resistant closure, containing 2 sachets each filled with 1 gram silica gel. Pack sizes: 120 tablets.

13. Manufacturer

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