2xxxxxx

1. NAME OF THE MEDICINAL PRODUCT

PROLAVIR LR (Lopinavir and Ritonavir Film Coated Tablets USP 200 mg/50 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Lopinavir USP 200 mg

Ritonavir USP 50mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow colored, film coated oval shaped biconvex tablets debossed with "LA58" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lopinavir/Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD_4 cell counts in a controlled study of Lopinavir/Ritonavir of 48 weeks duration, and in smaller uncontrolled dose-ranging studies of Lopinavir/Ritonavir of 72 weeks (for oral solution) and 144-360 weeks (for tablets) duration. At present, there are no results from controlled trials evaluating the effect of Lopinavir/Ritonavir on clinical progression of HIV.

Once daily administration of Lopinavir/Ritonavir has not been studied in therapy experienced patients.

4.2 Posology and method of administration

- ***Adults***

Oral Solution

The recommended dosage of Lopinavir/Ritonavir is 400/100 mg (5.0 mL) twice daily taken with food.

Concomitant Therapy

Efavirenz or Nevirapine

A dose increase of Lopinavir/Ritonavir to 533/133 mg (6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions and/or PRECAUTIONS**).

Film Coated Tablets

Lopinavir/Ritonavir tablets may be taken with or without food. The tablets should be swallowed whole and not chewed, broken or crushed.

The recommended oral dose of Lopinavir/Ritonavir tablets is as follows:

- Lopinavir/ritonavir 400/100 mg (given as two (2) 200/50mg tablets) twice daily
- Lopinavir/ritonavir 800/200 mg (given as four (4) 200/50mg tablets) once daily in patients with less than three lopinavir-associated mutations. There are insufficient data to support the use of once daily administration of lopinavir/ritonavir for adult patients with three or more lopinavir-associated mutations.

Lopinavir/ritonavir should not be administered once daily in combination with carbamazepine, Phenobarbital, or phenytoin **(**see **Drug interactions).**

Concomitant Therapy

Omeprazole and Ranitidine

Lopinavir/Ritonavir tablets can be used in combination with acid reducing agents (omeprazole and ranitidine) with no dose adjustment.

Efavirenz, Nevirapine, Amprenavir, or Nelfinavir

A dose increase of Lopinavir/Ritonavir tablets to 500/125mg twice daily (such as two 200/50 mg tablets and one 100/25mg tablet) should be considered when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir in treatment-experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) **(**see **Drug interactions).**

- ***Pediatric Patients***

Oral Solution

In children six months to 12 years of age, the recommended dosage of Lopinavir/Ritonavir oral solution is 12/3 mg/kg for those seven to less than 15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2); twice daily taken with food, up to a maximum dose of 400/100 mg in children greater than 40 kg (5.0 mL) twice daily. It is preferred that the prescriber calculate the appropriate milligram dose for each individual child less than or equal to 12 years old and determine the corresponding volume of solution. However, as an alternative the following table contains dosing guidelines for Lopinavir/Ritonavir oral solution based on body weight.

Concomitant Therapy

Efavirenz or Nevirapine

A dose increase of Lopinavir/Ritonavir oral solution to 13/3.25 mg/kg for those 7 to less than 15 kg and 11/2.75 mg/kg for those 15 to 45 kg (approximately equivalent to 300/75 mg/m^2) twice daily taken with food, up to a maximum dose of 533/133 mg in children greater than 45 kg twice daily should be considered when used in combination with efavirenz or nevirapine in treatment experienced children six months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). The following table contains dosing guidelines for Lopinavir/Ritonavir oral solution based on body weight, when used in combination with efavirenz or nevirapine in children (see CLINICAL PHARMACOLOGY: Drug-Drug Interactions and/or PRECAUTIONS).

Lopinavir/ritonavir should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

Dosing Guidelines Using Body Surface Area (m^2)

Oral Solution

Pediatric use (six months of age and above): the recommended dosage of Lopinavir/Ritonavir is 230/57.5.mg/m^2 twice daily taken with food, up to a maximum dose of 400/100 mg twice daily. The 230/57.5 mg/m^2 dosage might be insufficient in some children when coadministered with nevirapine or efavirenz. An increase of the dose of Lopinavir/Ritonavir to 300/75 mg/m^2 should be considered in these patients. Dose should be administered using a calibrated oral dosing syringe.

Use of Oral Solution with a feeding tube

The prescribed dose of lopinavir/ritonavir oral solution can be administered via a feeding tube. Follow the instructions for the feeding tube to administer the medicine. Products containing alcohol, like lopinavir/ritonavir, are not recommended for use with polyurethane feeding tubes due to potential incompatibility.

Film-coated tablets

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 or (fos)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 tables below. Lopinavir/Ritonavir oral solution is available for children with a BSA less than 0.6 m^2 or those who are unable to reliably swallow a tablet.

Body surface area can be calculated with the following equation:

*BSA (m^2) = SQR RT [Height (cm) X Weight (kg)] / 3600

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

Pediatric Dosing Guidelines Based on BSA Without Concomitant Efavirenz, Nevirapine, Nelfinavir or Amprenavir	
Body Surface Area* (m^2)	Recommended number of 100/25mg Tablet Twice daily
≥ 0.6 to <0.9	2 tablets (200/50mg)
≥ 0.9 to <1.4	3 tablets (300/75mg)
≥ 1.4	4 tablets (400/100mg)

Concomitant Therapy : Efavirenz, Nevirapine, Nelfinavir or Amprenavir

The following table contains dosing guidelines for Lopinavir/Ritonavir 100/25mg 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)	Recommended number of 100/25mg Tablet Twice daily
≥ 0.6 to <0.8	2 tablets (200/50 mg)
≥0.8 to <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 100/25mg Tablets Twice Daily
7 to < 15kg	Tablets are not recommended. Use oral solution.
15 to 25kg	2
> 25 to 35kg	3
> 35kg	4*
* Alternatively, two 200/50 mg tablets may be used for this dose in those patients who can swallow the larger tablet	

The following table contains dosing guidelines for lopinavir/ritonavir 100/25mg tablets based on 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 100/25mg Tablets Twice Daily
7 to < 15kg	Tablets are not recommended. Use oral solution.
15 to 20kg	2
> 20 to 30kg	3
> 30 to 45kg	4*
> 45kg	5
* Alternatively, two 200/50 mg tablets may be used for this dose in those patients who can swallow the larger tablet	

Pregnancy and postpartum

- No dose adjustment is required for lopinavir/ritonavir during pregnancy and postpartum.
- Once daily administration of lopinavir/ritonavir is not recommended for pregnant women due to the lack of pharmacokinetic and clinical data.

Note:

a) An oral solution formulation is available in the market for other brands.

b) PROLAVIR LR (Lopinavir and Ritonavir Film Coated Tablets USP 200 mg/50 mg) is available at the strength of 200 mg/50 mg only and may not be able to deliver all the dosing recommendations mentioned above. In such cases, other approved strengths should be used.

4.3 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 below table.

Drugs which should not be co-administered with Lopinavir/ritonavir	
Drug Class	**Drug Within Class Not to be Co-administered**
Alpha1-adrenoreceptor antagonist	alfuzosin HCL
Antianginal	ranolazine
Antiarrhythmic	dronedarone
Antibiotics	fusidic acid
Anticancer Agents	neratinib, apalutamide
Antigout	Colchicine in patients with renal and/or hepatic impairment
Antihistamines	astemizole, terfenadine
Antipsychotics	Blonanserin, lurasidone, pimozide
Benzodiazepines	midazolam, triazolam
Ergot derivatives	ergotamine, dihydroergotamine, ergonovine, methylergonovine
GI motility agent	cisapride
Herbal Product	St. John's Wort (*Hypericum perforatum)*
Hepatitis C direct acting antiviral	Elbasvir/grazoprevir
Lipid-modifying agents HMG-CoA Reductase Inhibitors Microsomal triglyceride transfer protein (MTTP) Inhibitor	 lovastatin, simvastatin lomitapide
long acting beta-adrenoceptor agonist	salmeterol
PDE5 enzyme inhibitor	sildenafil* (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH)
*see Warnings and Precautions and Drug Interactions for coadministration of sildenafil in patients with erectile dysfunction	

4.4 Special warnings and precautions for use

Drug Interactions

Lopinavir/ritonavir is an inhibitor of the P450 isoform CYP3A. Co-administration 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-Table, 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 co-administered with rifampin because large decreases in lopinavir concentrations may significantly decrease the therapeutic effect (See **DRUG INTERACTIONS**).

Co-administration of bedaquiline with strong CYP3A4 inhibitors may increase the systemic exposure of bedaquiline, which could potentially increase the risk of bedaquiline-related adverse reactions. Bedaquiline must be used cautiously with lopinavir/ritonavir, only if the benefit of co-administration outweighs the risk.

Co-administration of delamanid with a strong inhibitor of CYP3A (lopinavir/ritonavir) may slightly increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended.

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 inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone, or other glucocorticoids that are metabolized 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.

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, or injectable triamcinolone (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. Co-administration 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 co-administration 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 (See **CONTRAINDICATIONS**).

Caution should be exercised if HIV protease inhibitors, including lopinavir/ritonavir, are used concurrently 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, including rhabdomyolysis (See **DRUG INTERACTIONS**).

Tipranavir

In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, tipranavir (500 mg twice daily) with ritonavir (200 mg twice daily), co-administered with lopinavir/ritonavir (400/100 mg twice daily), resulted in a 55% and 70% reduction in lopinavir AUC and C_{min} respectively. The concomitant administration of lopinavir/ritonavir and tipranavir with low dose ritonavir is therefore not recommended.

Toxicity in Preterm Neonates

A safe and effective dose of lopinavir/ritonavir oral solution in the preterm neonate population has not been established. Lopinavir/ritonavir oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). Lopinavir/ritonavir oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities (See **WARNINGS AND PRECAUTIONS, Pediatric Use**). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at an increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients. Infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to lopinavir/ritonavir oral solution 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. Post-marketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving lopinavir/ritonavir oral solution.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance 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 occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, 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 to 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 observed. 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: Lipid Elevations**). 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. Pharmacokinetic data suggests increases in lopinavir plasma concentrations of approximately 30% as well as decreases in plasma protein binding in HIV and HCV co-infected patients with mild to moderate hepatic impairment (See **CLINICAL PHARMACOLOGY: Pharmacokinetics).** 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. These have been post-marketing 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-1 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 (See **CLINICAL PHARMACOLOGY: Microbiology**).

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. Rare 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.

Lipid Elevations

Treatment with lopinavir/ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides. 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 clinically 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 Grave's disease, polymyositis, and Guillain- Barré 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.

Geriatric Use

Clinical studies of lopinavir/ritonavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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. For Pediatric Use of Lopinavir/Ritonavir Solution, See **DOSAGE AND ADMINISTRATION**, **WARNINGS AND PRECAUTIONS**. In HIV-infected patients age six months to 18 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. Lopinavir/ritonavir should not be administered once daily in pediatric patients.

4.5 Interaction with other medicinal products and other forms of interaction

Lopinavir/ritonavir is an inhibitor of CYP3A both *in vitro* and *in vivo*. Co-administration 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. 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 are listed in Table under **CONTRAINDICATIONS**.

Lopinavir/ritonavir is metabolized by CYP3A. Co-administration of lopinavir/ritonavir and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect. Although not noted with concurrent ketoconazole, coadministration of lopinavir/ritonavir and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with lopinavir/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

Anti-HIV Agents

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

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.

Didanosine

It is recommended that didanosine be administered on an empty stomach; therefore, Didanosine should be given one hour before or two hours after lopinavir/ritonavir oral Solution (given with food). Didanosine may be co-administered with lopinavir/ritonavir tablets without food.

Zidovudine and Abacavir

Lopinavir/ritonavir induces glucuronidation, therefore lopinavir/ritonavir has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Tenofovir

A study has shown 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.

All

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

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine

No change in the pharmacokinetics of lopinavir was apparent in healthy adult subjects during nevirapine and lopinavir/ritonavir coadministration. Results from a study in HIV-positive pediatric subjects revealed a decrease in lopinavir concentrations during nevirapine co-administration. 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 clinical 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 or oral solution to 533/133 mg BID should be considered when co-administered with nevirapine. Lopinavir/ritonavir should not be administered once daily in combination with nevirapine.

Efavirenz

When used in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in multiple protease inhibitor-experienced subjects, increasing the dose of lopinavir/ritonavir 25% from 400/100mg (two (2) 200/50mg tablets) BID to 500/125mg (two (2) 200/50 tablets and one (1) 100/25 mg tablet) yielded similar lopinavir plasma concentrations as compared to historical data of lopinavir/ritonavir 400/100 mg BID.

For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase of lopinavir/ritonavir tablet to 500/125 mg BID or oral solution to 533/133 mg BID should be considered when co-administered with efavirenz. Increasing the dose of lopinavir/ritonavir tablets to 600/150 (three (3) tablets) BID co-administered with efavirenz significantly increased the lopinavir plasma concentrations approximately 36% and ritonavir concentrations approximately 56% to 92% 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.

Delavirdine

Delavirdine has the potential to increase plasma concentrations of lopinavir.

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.

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)

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. Lopinavir/ritonavir should not be administered once daily in combination with amprenavir.

Fosamprenavir

A study has shown that co-administration 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.

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.

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. The dose of lopinavir/ritonavir may need to be increased when co-administered with nelfinavir, particularly in HIV patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir.

Lopinavir/ritonavir should not be administered once daily in combination with nelfinavir.

Ritonavir

When lopinavir/ritonavir was co-administered with an additional 100 mg ritonavir twice daily, lopinavir AUC increased 33% and C_{min} increased 64% as compared to lopinavir/ritonavir 400/100 mg (three (3) soft gel capsules) twice daily.

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 400/100mg BID.

Lopinavir/ritonavir once daily has not been studied in combination with saquinavir.

Hepatitis C direct acting antivirals

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.

Glecaprevir/pibrentasvir:

Concomitant administration of glecaprevir/pibrentasvir and lopinavir/ritonavir is not recommended due to an increased risk of ALT elevations associated with increased GLE exposure.

Ombitasvir/paritaprevir/ritonavir and dasabuvir

Concentrations of ombitasvir, paritaprevir, and ritonavir may be increased when co-administered with lopinavir/ritonavir, therefore, co-administration is not recommended.

Simeprevir

Concomitant use of lopinavir/ritonavir and simeprevir may result in increased plasma concentrations of simeprevir. It is not recommended to co-administer lopinavir/ritonavir and simeprevir.

Sofosbuvir/velpatasvir/voxilaprevir:

Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and lopinavir/ritonavir is not recommended due to the potential for increased toxicity, which may negatively impact compliance

Telaprevir

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

HIV CCR5 antagonist:

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 400/100mg BID. For further details, see complete prescribing information for maraviroc.

Other Drugs

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.

Antiarrhythmics (amiodarone, bepridil, dronedarone (see CONTRAINDICATIONS), Systemic lidocaine and quinidine): Concentrations may be increased when coadministered with lopinavir/ritonavir. Caution is warranted and therapeutic concentration monitoring is recommended when available.

Digoxin*:* A literature report has shown that co-administration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when co-administering lopinavir/ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.

Anticancer Agents (e.g. abemaciclib, apalutamide, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vincristine, vinblastine):

May have their serum concentrations increased when co-administered with lopinavir/ritonavir resulting in the potential for increased adverse events, some of which may be serious. Coadministration of venetoclax or ibrutinib with lopinavir/ritonavir could increase venetoclax or ibrutinib exposure potentially resulting in a serious risk of tumor lysis syndrome. Coadministration of encorafenib or ivosidenib with lopinavir/ritonavir could increase encorafenib or ivosidenib exposure potentially increasing the risk of serious adverse events such as QT interval prolongation. For venetoclax, encorafenib, ibrutinib, ivosidenib nilotinib and dasatinib, refer to their prescribing information for dosing instructions. Coadministration of apalutamide is contraindicated with Lopinavir/Ritonavir since apalutamide may decrease exposure of Lopinavir/Ritonavir with potential loss of virologic response. In addition, co-administration of apalutamide and Lopinavir/Ritonavir may lead to increased exposure of apalutamide resulting in increased potential for adverse events including seizure.

Anticoagulants:

Warfarin concentrations may be affected when co-administered with lopinavir/ritonavir. It is recommended that INR (international normalized ratio) be monitored.

Rivaroxaban: Co-administration of rivaroxaban and lopinavir/ritonavir may increase rivaroxaban exposure which may increase the risk of bleeding.

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 lopinavir/ritonavir.

Lamotrigine and valproate: Co-administration of lopinavir/ritonavir and either of these drugs was associated with reduction in exposure of the anticonvulsants: 50% 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.

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.

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: A study has shown that co-administration of ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, 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.

Antigout Agents

Concentrations of colchicine are expected to increase when co-administered with lopinavir/ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir. Refer to the colchicine label for prescribing information.

Anti-infective

Moderate increases in clarithromycin AUC are expected when co-administered with lopinavir/ritonavir. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered.

Anti-mycobacterial

Rifabutin: When rifabutin and lopinavir/ritonavir were co-administered for ten days, rifabutin (parent drug and active 25-O-desacetyl metabolite) C_{max} and AUC wereincreased by 3.5- and 5.7-fold, respectively. On the basis of these data, a 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.

Rifampin: Due to large decreases in lopinavir concentrations, rifampin should not be used in combination with standard dose lopinavir/ritonavir. The use of Rifampin with standard dose 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 of up to 57% and with lopinavir/ritonavir 400/400 mg BID resulted in decreases of up to 7% 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 approximately 10 days prior to addition of rifampicin. Lopinavir/ritonavir dose should then be titrated upward. Close monitoring of liver function is indicated.

Bedaquiline: In a healthy volunteer drug interaction study of 400 mg single dose bedaquiline and lopinavir/ritonavir 400/100 mg twice daily for 24 days, bedaquiline exposures (AUC) were increased by 22%. Bedaquiline must be used cautiously with lopinavir/ritonavir, only if the benefit of co-administration outweighs the risk.

Delamanid: In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, exposures of delamanid and a delamanid metabolite, DM-6705, were slightly increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (**See WARNINGS AND PRECAUTIONS: Drug Interactions**).

Antiparasitic

Decreases in the therapeutic concentration of atovaquone are possible when co-administered with lopinavir/ritonavir. Increases in atovaquone doses may be necessary.

Antipsychotics

Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase. Refer to quetiapine prescribing information for dosing instructions (**See WARNINGS AND PRECAUTIONS: Drug Interactions**).

Corticosteroids

Dexamethasone may induce 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 metabolized 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, budesonide, and injectable triamcinolone, particularly for long-term use (**See WARNINGS AND PRECAUTIONS: Drug Interactions**).

Dihydropyridines Calcium Channel Blockers

(e.g. felodipine, nifedipine, nicardipine): May have their serum concentrations increased by lopinavir/ritonavir.

Disulfiram/Metronidazole

Lopinavir/ritonavir oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction, such as metronidazole.

PDE5 inhibitors

Avanafil: Co-administration of lopinavir/ritonavir with avanafil is expected to result in large increases in avanafil exposure and is not recommended (**See WARNINGS AND PRECAUTIONS: Drug Interactions**).

Sildenafil: Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events (**See WARNINGS AND PRECAUTIONS: Drug Interactions**).

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: Drug Interactions**).

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: Drug Interactions**).

GnRH Receptor Antagonists

Elagolix: Coadministration of elagolix with lopinavir/ritonavir could increase elagolix exposure through inhibition of OATP, CYP 3A, and P-gp. Known serious adverse events for elagolix include suicidal ideation and hepatic transaminase elevations. In addition, elagolix is a weak/moderate inducer of CYP3A, which may decrease exposure of lopinavir/ritonavir. Refer to the elagolix label for dosing information with strong CYP-3A4 inhibitors.

Kinase Inhibitors (also see anticancer agents above)

Fostamatinib: Coadministration of fostamatinib with lopinavir/ritonavir could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia.

Herbal Products

Patients on lopinavir/ritonavir should not use products containing St Johns 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 WARNINGS AND PRECAUTIONS: Drug Interactions**).

HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered 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 concurrently with lopinavir/ritonavir, a mean 4.7-fold and 5.9-fold increase in atorvastatin C_{max} and AUC, respectively, 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: Drug Interactions**).

Lomitapide

Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated.

Immunosuppressants

Concentrations of these drugs (e.g. cyclosporine, tacrolimus and sirolimus (rapamycin)) may be increased when co-administered with lopinavir/ritonavir. More frequent therapeutic concentration monitoring is recommended until blood levels of these products have stabilized.

Methadone

Lopinavir/ritonavir was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Oral Contraceptives 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.

Vasodilating agents

Co-administration of bosentan and lopinavir/ritonavir increased steady-state bosentan maximum concentrations (C_{max}) and area-under-the-curve (AUC) by 6-fold and 5–fold, respectively. Refer to the bosentan label for prescribing information.

Clinically Significant Drug Interactions Are Not Expected

Drug interaction studies reveal no clinically significant interaction between desipramine (CYP2D6 probe), omeprazole or ranitidine.

Clinical studies showed no clinically significant interaction between lopinavir/ritonavir and raltegravir.

Based on known metabolic profiles, clinically 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Human Data

Risk Summary:

Lopinavir/ritonavir has been evaluated in 3,366 women during pregnancy.

Available human data suggest that lopinavir/ritonavir does not increase the risk of overall major birth defects compared to the background rate. Lopinavir/ritonavir can be used during pregnancy if clinically needed.

Antiretroviral Pregnancy Registry:

In post-marketing surveillance through the Antiretroviral Pregnancy Registry, established since January 1989, no increased risk of birth defects has been reported among over 1000 women exposed to lopinavir/ritonavir in 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.

Clinical Trials:

In an open-label pharmacokinetic study, 12 HIV-infected pregnant women who were less than 20 weeks of gestation and on combination antiretroviral therapy initially received lopinavir/ritonavir 400 mg/100 mg (two 200/50 mg tablets) twice daily up to a gestational age of 30 weeks. At 30 weeks age of gestation, the dose was increased to 500/125 mg (two 200/50 mg tablets plus one 100/25 mg tablet) twice daily until subjects were 2 weeks postpartum.

Except for two reported TEAEs (anemia in a zidovudine and penicillin-treated patient, and H1N1 influenza), no other serious adverse events and deaths were reported. All subjects tolerated the dose increase, with no premature discontinuations.

In another open-label pharmacokinetic study, 19 HIV-infected pregnant women received lopinavir/ritonavir 400/100 mg twice daily as part of combination antiretroviral therapy during pregnancy from before conception. Laboratory abnormalities included 2 cases of Grade 3 increases in ALT. Pregnancy related events included 1 case of preeclampsia, 6 preterm deliveries, 7 cases of low birth weight infants (<2500 grams), and 2 stillbirths. No deaths, serious adverse events or discontinuations due to adverse events were reported. Seventeen of 19 patients had HIV RNA < 50 copies/mL at delivery.

Animal Data

Lopinavir in combination with ritonavir at a 2 to1 ratio produced no effects on fertility in male and female rats at maximum achievable doses producing drug exposures which were comparable to or slightly less than those achieved with the recommended therapeutic dose. Levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

No treatment-related malformations were observed when lopinavir/ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicity observed in rats (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicity was observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6- fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

Lactation

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving lopinavir/ritonavir. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be informed that nausea has been reported during treatment with Lopinavir and Ritonavir tablets.

4.8 Overdose

Overdoses with lopinavir/ritonavir oral solution have been reported. The following events have been reported in association with unintended overdoses in preterm neonates: complete AV block, cardiomyopathy, lactic acidosis, and acute renal failure. Healthcare professionals should be aware that lopinavir/ritonavir oral solution is highly concentrated and contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v), and therefore, should pay special attention to accurate calculation of the dose of lopinavir/ritonavir, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors and overdose. This is especially important for infants and young children.

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 activated charcoal may also be used to aid in removal of unabsorbed drug. Since lopinavir/ritonavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug. However, dialysis can remove both alcohol and propylene glycol in the case of overdose with lopinavir/ritonavir oral solution.

4.9 Undesirable effects (Adverse Reactions)

Adults

Treatment-Emergent Adverse Reactions

The safety of lopinavir/ritonavir has been investigated in over 2,600 patients in Phase II-IV clinical trials, of which more than 700 have received a dose of 800/200 mg (6 capsules or 4 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies, lopinavir/ritonavir was used in combination with efavirenz or nevirapine. 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. The following have been identified as adverse reactions of moderate or severe intensity:

Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult Patients Receiving lopinavir/ritonavir in Combined Phase II/IV Studies (N=2,612)

System Organ Class (SOC) and Adverse Reaction	n	%
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
anemia*	54	2.067
leukopenia and neutropenia*	44	1.685
lymphadenopathy*	35	1.340
CARDIAC DISORDERS		
atherosclerosis such as myocardial infarction*	10	0.383
atrioventricular block*	3	0.115
tricuspid valve incompetence*	3	0.115
EAR AND LABYRINTH DISORDERS		
vertigo*	7	0.268
tinnitus	6	0.23
ENDOCRINE DISORDERS		
hypogonadism*	16	0.785[1]
EYE DISORDERS		
visual impairment*	8	0.306
GASTROINTESTINAL DISORDERS		
diarrhea*	510	19.525
nausea	269	10.299
vomiting*	177	6.776
abdominal pain (upper and lower)*	160	6.126
gastroenteritis and colitis*	66	2.527
dyspepsia	53	2.029
pancreatitis*	45	1.723
Gastroesophageal Reflux Disease (GERD)*	40	1.531
hemorrhoids	39	1.493
flatulence	36	1.378
abdominal distension	34	1.302
constipation*	26	0.995
stomatitis and oral ulcers*	24	0.919
duodenitis and gastritis*	20	0.766
gastrointestinal hemorrhage including rectal hemorrhage*	13	0.498
dry mouth	9	0.345
gastrointestinal ulcer*	6	0.23
fecal incontinence	5	0.191
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
fatigue including asthenia*	198	7.580
HEPATOBILIARY DISORDERS		
hepatitis including AST, ALT, and GGT increases*	91	3.484
hepatomegaly	5	0.191
cholangitis	3	0.115
hepatic steatosis	3	0.115
IMMUNE SYSTEM DISORDERS		
hypersensitivity including urticaria and angioedema*	70	2.680
immune reconstitution syndrome	3	0.115
INFECTIONS AND INFESTATIONS		
upper respiratory tract infection*	363	13.897
lower respiratory tract infection*	202	7.734
skin infections including cellulitis, folliculitis, and furuncle*	86	3.292
METABOLISM AND NUTRITION DISORDERS		
hypercholesterolemia*	192	7.351
hypertriglyceridemia*	161	6.164
weight decreased*	61	2.335
decreased appetite	52	1.991
blood glucose disorders including diabetes mellitus*	30	1.149
weight increased*	20	0.766
lactic acidosis*	11	0.421
increased appetite	5	0.191
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
musculoskeletal pain including arthralgia and back pain*	166	6.355
myalgia*	46	1.761
muscle disorders such as weakness and spasms*	34	1.302
rhabdomyolysis*	18	0.689
osteonecrosis	3	0.115
NERVOUS SYSTEM DISORDERS		
headache including migraine*	165	6.317
insomnia*	99	3.79
neuropathy and peripheral neuropathy*	51	1.953
dizziness*	45	1.723
ageusia*	19	0.727
convulsion*	9	0.345
tremor*	9	0.345
cerebral vascular event*	6	0.230
PSYCHIATRIC DISORDERS		
anxiety*	101	3.867
abnormal dreams*	19	0.727
libido decreased	19	0.727
RENAL AND URINARY DISORDERS		
renal failure*	31	1.187
hematuria*	20	0.766
nephritis*	3	0.115
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
erectile dysfunction*	34	1.668[1]
menstrual disorders - amenorrhea, menorrhagia*	10	1.742[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
rash including maculopapular rash*	99	3.790
dermatitis/rash including eczema and seborrheic dermatitis*	50	1.914
night sweats*	42	1.608
pruritus*	29	1.110
alopecia	10	0.383
capillaritis and vasculitis*	3	0.115
VASCULAR DISORDERS		
hypertension*	47	1.799
deep vein thrombosis*	17	0.651

*Represents a medical concept including several similar MedDRA PTs

[1]. Percentage of male population (N=2,038)

[2]. Percentage of female population (N=574)

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy including lopinavir/ritonavir with Grade 3 to 4 laboratory abnormalities are presented in **below tables.**

Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Antiretroviral-Naïve Patients

		Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 weeks)	Study 730 (48 weeks)	
Variable	**Limit[1]**	**lopinavir/ritonavir 400/100 mg BID + d4T +3TC (N=326)**	**Nelfinavir 750 mg TID + d4T + 3TC (N=327)**	**lopinavir/ritonavir 800/200 mg QD + TDF + FTC (N=115)**	**lopinavir/ritonavir 400/100 mg BID + TDF + FTC (N=75)**	**lopinavir/ritonavir BID + d4T + 3TC (N=100)**	**LPV/r QD + TDF + FTC (N=333)**	**LPV/r BID + TDF + FTC (N=331)**
Chemistry	**High**							
Glucose	>250 mg/dL	2%	2%	3%	1%	4%	0%	< 1%
Uric Acid	>12 mg/dL	2%	2%	0%	3%	5%	< 1%	1%
SGOT/AST[2]	>180 U/L	2%	4%	5%	3%	10%	1%	2%
SGPT/ALT[2]	>215 U/L	4%	4%	4%	3%	11%	1%	1%
GGT	>300 U/L	N/A	N/A	N/A	N/A	10%	N/A	N/A
Total Cholesterol	>300 mg/dL	9%	5%	3%	3%	27%	4%	3%
Triglycerides	>750 mg/dL	9%	1%	5%	4%	29%	3%	6%
	>2 x ULN	3%	2%	7%	5%	4%	N/A	N/A
Amylase								
Lipase	>2x ULN	NA	NA	NA	NA	NA	3%	5%
Chemistry	Low							
Calculated Creatinine Clearance	<50 mL/min	NA	NA	NA	NA	NA	2%	2%
Hematology	Low							
Neutrophils	0.75 x 109/L	1%	3%	5%	1%	5%	2%	1%

1 ULN = upper limit of the normal range; N/A = Not Applicable.

2 Criterion for Study 730 was >5x ULN.(AST/ALT)

Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult antiretroviral -Experienced Patients

		Study 888 (48 Weeks)		Study 957[2] and Study 765[3] (84-144 Weeks)	Study 802 (48 weeks)	
Variable	**Limit[1]**	**Lopinavir/ritonavir 400/100mg BID + NVP + NRTIs (N=148)**	**Investigator-selected protease inhibitor(s) + NVP + NRTIs (N=140)**	**Lopinavir/ritonavir BID + NNRTI + NRTIs (N=127)**	**LPV/r 800/200mg Once Daily +NRTIs (N=300)**	**LPV/r 400/100mg Twice Daily +NRTIs (N=299)**
Chemistry	**High**					
Glucose	>250 mg/dL	1%	2%	5%	2%	2%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%	1%	1%
SGOT/AST4	>180 U/L	5%	11%	8%	3%	2%
SGPT/ALT4	>215 U/L	6%	13%	10%	2%	2%
GGT	>300 U/L	N/A	N/A	29%	N/A	N/A
Total Cholesterol	>300 mg/dL	20%	21%	39%	6%	7%
Triglycerides	>750 mg/dL	25%	21%	36%	5%	6%
Amylase	>2 x ULN	4%	8%	8%	4%	4%
Lipase	>2 x ULN	N/A	N/A	N/A	4%	4%
Creatine Phosphokinase	>4 x ULN	N/A	N/A	N/A	4%	5%
Chemistry	**Low**					
Calculated creatinine clearance	<50 ml/min	N/A	N/A	N/A	3%	3%
Inorganic Phosphorus	<1.5 mg/dL	1%	0%	2%	1%	<1%
Hematology	Low					
Neutrophils	0.75x 10^9/L	1%	2%	4%	3%	4%
Hemoglobin	<80 g/L	1%	1%	1%	1%	2%

1. ULN = upper limit of the normal range; N/A = Not Applicable.
2. Includes clinical laboratory data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 84 weeks. Patients received lopinavir/ritonavir in combination with NRTIs and efavirenz.
3. Includes clinical laboratory data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 144 weeks. Patients received lopinavir/ritonavir in combination with NRTIs and nevirapine.
4. Criterion for Study 802 was >5x ULN (AST/ALT).

ADR - Pediatrics

Treatment-Emergent Adverse Events

Lopinavir/ritonavir has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

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 for up to 48 weeks in Study M98-940. A total of 8 children experienced moderate or severe adverse events at least possibly related to lopinavir/ritonavir. Rash (reported in 3%) was the only drug-related clinical adverse event of moderate to severe intensity observed in greater than or equal to 2% of children enrolled.

Lopinavir/Ritonavir oral solution dosed at 300/75 mg/m^2 has been studied in 31 pediatric patients 14 days to 6 months of age. The adverse reaction profile in Study 1030 was similar to that observed in older children and adults. No adverse reaction was reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included decreased neutrophil count (N=3), anemia (N=2), high potassium (N=2), and low sodium (N=2).

Laboratory Abnormalities

The percentages of pediatric patients ages 6 months to 12 years or treated with combination therapy including lopinavir/ritonavir in Study M98-940 with Grade 3 to 4 laboratory abnormalities are presented in **below table.**

Grade 3 to 4 Laboratory Abnormalities Reported in Greater Than or Equal to 2% Pediatric Patients

Variable	**Limit[+]**	**Lopinavir/ritonavir BID + RTIs (N = 100)**
Chemistry	**High**	
Sodium	>149 mEq/L	3.0%
Total bilirubin	> 2.9 x ULN	3.0%
SGOT/AST	> 180 U/L	8.0%
SGPT/ALT	> 215 U/L	7.0%
Total Cholesterol	>300 mg/dL or >7.77 mmol/L	3.0%
Amylase	> 2.5 x ULN	7.0%[++]
Chemistry	**Low**	
Sodium	< 130 mEq/L	3.0%
Hematology	**Low**	
Platelet Count	< 50 x 10^9/L	4.0%
Neutrophils	< 0.40 x 10^9/L	2.0%

[+]ULN = upper limit of the normal range.

[++]Subjects with Grade 3 to 4 amylase confirmed by elevations in pancreatic amylase.

ADR - Postmarketing Experience

Hepatobiliary disorders: Hepatitis has been reported in patients on lopinavir/ritonavir therapy.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme have been reported.

Cardiac disorders: Bradyarrhythmia has been reported.

Renal and urinary disorders: Nephrolithiasis

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Microbiology

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.

Antiviral activity in vitro

The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10 to 27 nM (0.006 to 0.017 mcg/mL, 1 mcg/mL equals 1.6 microM) and ranged from 4 to 11 nM (0.003 to 0.007 mcg/mL) against several HIV-1 clinical isolates (n equals 6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 to 289 nM (0.04 to 0.18 mcg/mL), representing a 7-to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in-vitro*.

The selection of resistance to lopinavir/ritonavir in antiretroviral treatment naive patients has not yet been characterized. In a Phase III study of 653 antiretroviral treatment naive patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV greater than 400 copies/mL at week 24, 32, 40 and/or 48 were analyzed. No evidence of genotypic or phenotypic resistance to lopinavir/ritonavir was observed in 37 evaluable lopinavir/ritonavir -treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to lopinavir/ritonavir in antiretroviral treatment naïve pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

Resistance to lopinavir/ritonavir has been noted to emerge in patients treated with other protease inhibitors prior to lopinavir/ritonavir therapy. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (greater than 400 copies/mL) viral RNA following treatment with lopinavir/ritonavir for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least four mutations associated with protease inhibitor resistance immediately prior to lopinavir/ritonavir therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on lopinavir/ritonavir therapy. The assessment of these mutational patterns is under study.

Cross Resistance

Preclinical Studies

Varying degrees of cross-resistance have been observed among protease inhibitors. The in-vitro activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed greater than 4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed less than 4-fold reduced susceptibility to lopinavir. Isolates with greater than 4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the clinical section below (see ***Clinical Studies:*** *Antiviral Activity of lopinavir/ritonavir in Patients With Previous Protease Inhibitor Therapy*).

Cross-Resistance During lopinavir/ritonavir Therapy

Little information is available on the cross-resistance of viruses selected during therapy with lopinavir/ritonavir. Isolates from four patients previously treated with one or more protease inhibitors that developed increased lopinavir phenotypic resistance during lopinavir/ritonavir therapy either remained cross-resistant or developed cross-resistance to ritonavir, indinavir, and nelfinavir. All rebound viruses either remained fully sensitive or demonstrated modestly reduced susceptibility to amprenavir (up to 8.5-fold concurrent with 99-fold resistance to lopinavir). The rebound isolates from the two subjects with no prior saquinavir treatment remained fully sensitive to saquinavir.

Genotypic correlates of reduced virologic response in antiretroviral-experienced patients initiating a lopinavir/ritonavir-based combination regimen

Virologic response to lopinavir/ritonavir has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. Below table shows the 48-week virologic response (HIV RNA <400 copies/mL) according to the number of the above protease inhibitor resistance mutations at baseline in studies 888 and 765 and study 957 (see below).

Virologic Response (HIV RNA <400 copies/mL) at Week 48 by Baseline Lopinavir/ritonavir Susceptibility and by Number of Protease Substitutions Associated with Reduced Response to Lopinavir/ritonavir[1]

Number of protease inhibitor mutations at baseline[1]	**Study 888 (Single protease inhibitor-experienced[2], NNRTI-naïve) n=130**	**Study 765 (Single protease inhibitor-experienced[3], NNRTI-naïve) n=56**	**Study 957 (Multiple protease inhibitor-experienced[4], NNRTI-naïve) n=50**
0-2	76/103 (74%)	34/45 (76%)	19/20 (95%)
3-5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	n/a	1/4 (25%)

1. Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.
2. 43% indinavir, 42% nelfinavir, 10% ritonavir, 15% saquinavir.
3. 41% indinavir, 38% nelfinavir, 4% ritonavir, 16% saquinavir.
4. 86% indinavir, 54% nelfinavir, 80% ritonavir, 70% saquinavir

Below table shows the 48-week virologic response (HIV-1 RNA <50 copies/mL) in study 802 according to the number of lopinavir-associated resistance mutations listed in above **Table** present at baseline. There are insufficient data to support once daily administration of lopinavir/ritonavir for adult patients with three or more lopinavir-associated mutations.

Virologic Response (HIV-1 RNA <50 copies/mL) at Week 48 by Baseline Number of Protease Substitutions Associated with Reduced Response to Lopinavir/ritonavir

Number of protease Inhibitor substitutions at baseline[1]	**Study 802 (Treatment-experienced[2]) LPV/r Once Daily + NRTIs n=268**	**Study 802 (Treatment-experienced[3]) LPV/r Twice Daily + NRTIs n=264**
0-2	167/255 (65%)	154/250 (62%)
3-5	4/13 (31%)	8/14 (57%)
6 or more	N/A	N/A

1. Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.
2. 88% NNRTI-experienced, 47% PI-experienced (24% nelfinavir, 19% indinavir, 13% atazanavir).
3. 81% NNRTI-experienced, 45% PI-experienced (20% nelfinavir, 17% indinavir, 13% atazanavir).

Clinical Studies

Antiviral Activity of lopinavir/ritonavir in Patients With Previous Protease Inhibitor Therapy

The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to lopinavir/ritonavir therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naive patients with HIV RNA greater than 1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir, and ritonavir (Study M98-957). In this study, patients were initially randomized to receive one of two doses of lopinavir/ritonavir in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC_{50} values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC_{50} against wild-type HIV. Fifty-five percent (31/56) of these baseline isolates displayed a greater than 4-fold reduced susceptibility to lopinavir. These 31 isolates had a mean reduction in lopinavir susceptibility of 27.9-fold.

After 48 weeks of treatment with lopinavir/ritonavir, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA less than or equal to 400 copies/mL was observed in 93% (25/27), 73% (11/15), and 25% (2/8) of patients with less than or equal to 10-fold, greater than 10 and less than 40 fold, and greater than or equal to 40-fold reduced susceptibility to lopinavir at baseline, respectively. Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic. Plasma HIV RNA less than or equal to 50 copies/mL was observed in 81% (22/27), 60% (9/15), and 25% (2/8) in the above groups of patients, respectively.

There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on lopinavir/ritonavir therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of lopinavir/ritonavir 400/100 mg BID 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 BID. The *in vitro* antiviral EC_{50} of lopinavir is approximately 10- fold lower than that of ritonavir. Therefore, the antiviral activity of Lopinavir/Ritonavir is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir capsules after lopinavir/ritonavir 400/100 mg BID with food for three weeks from a pharmacokinetic study in HIV-infected adult subjects (n=19).

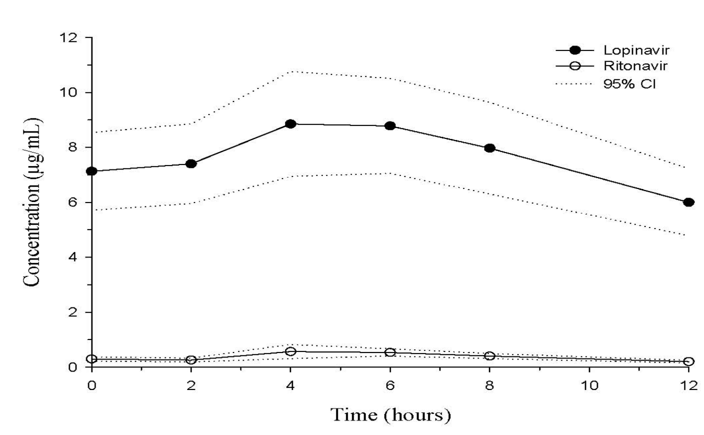

Figure 1 Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (N = 19)

Absorption

Capsules

In a pharmacokinetic study in HIV-positive subjects (n=19), multiple dosing with 400/100 mg Lopinavir/Ritonavir BID with food for three weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 mcg/mL, occurring approximately four hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 mcg/mL and minimum concentration within a dosing interval was 5.5 ± 2.7 mcg/mL. Lopinavir AUC over a 12-hour dosing interval averaged 92.6 ± 36.7 mcg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Under non-fasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of Lopinavir/Ritonavir co-formulated soft gel capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the Lopinavir/Ritonavir liquid relative to the capsule formulation.

Tablets

In a pharmacokinetic study in HIV-positive subjects (n=18), multiple dosing with 400/100 mg Lopinavir/Ritonavir BID with or without food for two weeks produced a mean ± SD lopinavir C_{max} of 12.3 ± 5.4 mcg/mL, occurring approximately four hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 mcg/mL and minimum concentration within a dosing interval was 5.6 ± 4.5 mcg/mL. Lopinavir AUC over a 12-hour dosing interval averaged 113.2 ± 60.5 mcg•h/mL. The absolute bioavailability of lopinavir coformulated with ritonavir in humans has not been established.

Effects of Food on Oral Absorption

Oral Solution

Lopinavir/Ritonavir co-formulated soft gel capsules and liquid were bioequivalent under nonfasting conditions (moderate fat meal). Administration of a single 400/100 mg dose of Lopinavir/Ritonavir soft gel capsules with a moderate fat meal (500 to 682 kcal, 23 to 25% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max}, respectively, relative to fasting. For Lopinavir/Ritonavir oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54%, respectively. Relative to fasting, administration of Lopinavir/Ritonavir with a high fat meal (872 kcal, 56% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively, for soft gel capsules, and 130 and 56%, respectively, for oral solution. To enhance bioavailability and minimize pharmacokinetic variability Lopinavir/Ritonavir should be taken with food.

Tablets

Administration of a single 400/100 mg dose of lopinavir/ritonavir tablets under fed conditions (high-fat, 872 kcal, 56% from fat) compared to the fasted state was associated with no significant changes in C_{max} and AUC therefore, lopinavir/ritonavir tablets may be taken with or without food. Lopinavir/ritonavir tablets have also shown less pharmacokinetic variability under all meal conditions compared to the lopinavir/ritonavir capsule.

Distribution

At steady state, lopinavir is approximately 98 to 99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin, however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg lopinavir/ritonavir BID, and is similar between healthy volunteers and HIV-positive patients.

Metabolism

In vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor, which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A 14C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg lopinavir/ritonavir dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Excretion

Following a 400/100 mg 14C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of 14C-lopinavir can be accounted for in urine and feces, respectively, after eight days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5.98 +/- 5.75 L/hr (mean +/- SD, N=19).

Pharm - PK – Pediatric

Data from the P1030 clinical trial in children below 2 years of age include the pharmacokinetics of Lopinavir/Ritonavir 300/75 mg/m2 twice daily studied in a total of 31 pediatric patients, ranging in age from 14 days to 6 months. In a study of 9 patients aged 14 days to 6 weeks the lopinavir mean AUC12, C_{max}, and C_{min} were 43.39 ± 14.8 µg•h/ml, 5.17 ± 1.84 µg/ml, and 1.40 ± 0.48 µg/ml, respectively. In 18 patients aged 6 weeks to 6 months the lopinavir AUC12, C_{max}, and C_{min} were 74.50 ± 37.87 µg•h/ml, 9.39 ± 4.91 µg/ml, 1.95 ± 1.80 µg/ml, respectively.

In the M98-940 study, the pharmacokinetics of lopinavir/ritonavir 300/75 mg/m2 BID and 230/57.5 mg/m2 BID have been studied in a total of 53 pediatric patients, ranging in age from six months to 12 years. The 230/57.5 mg/m2 BID regimen without nevirapine and the 300/75 mg/m2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine). Lopinavir/ritonavir once daily has not been evaluated in pediatric patients. The lopinavir mean steady-state AUC, C_{max}, and Cmin were 72.6 ± 31.1mcg• h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 mcg/mL, respectively after lopinavir/ritonavir 230/57.5 mg/m2 BID without nevirapine (n=12), and were 85.8 ± 36.9 mcg• h/mL, 10.0 ± 3.3 and 3.6 ± 3.5 mcg/mL, respectively after 300/75 mg/m2 BID with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BID (six months to eight years) or 4 mg/kg BID (greater than eight years).

Once Daily Dosing

Capsules

The pharmacokinetics of once daily Lopinavir/Ritonavir have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Lopinavir/Ritonavir 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once daily regimen. Multiple dosing of 800/200 mg Lopinavir/Ritonavir once daily for 4 weeks with food (n = 24) produced a mean ± SD lopinavir C_{max} of 11.8 ± 3.7 µg/mL, occurring approximately 6 hours after administration.

The mean steady-state lopinavir trough concentration prior to the morning dose was 3.2 ± 2.1 µg/mL and minimum concentration within a dosing interval was 1.7 ± 1.6 µg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 154.1 ± 61.4 µg•h/mL.

Tablets

The pharmacokinetics of once daily lopinavir/ritonavir have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Lopinavir/ritonavir 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once daily regimen. Multiple dosing of 800/200 mg lopinavir/ritonavir once daily for 2 weeks without meal

restriction (n = 16) produced a mean ± SD lopinavir C_{max} of 14.8 ± 3.5µg/mL, occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 5.5 ± 5.4 µg/mL and minimum concentration within a dosing interval was 3.2 ± 3.4 µg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 206.5 ± 89.7 µg•h/mL.

Effects on Electrocardiogram

QTcF interval was evaluated in a randomized, 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) msec and 13.1(15.8) msec for 400/100 mg twice-daily and supratherapeutic 800/200 mg twice-daily lopinavir/ritonavir, 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 lopinavir/ritonavir doses at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving lopinavir/ritonavir in the same study on Day 3. Maximum PR interval was 286 msec and no second or third degree heart block was observed.

Special Populations

Pregnancy

In an open-label pharmacokinetic study, 12 HIV-infected pregnant women who were less than 20 weeks of gestation and on combination antiretroviral therapy initially received lopinavir/ritonavir 400 mg/100 mg (two 200/50 mg tablets) twice daily up to a gestational age of 30 weeks. At 30 weeks age of gestation, the dose was increased to 500/125 mg (two 200/50 mg tablets plus one 100/25 mg tablet) twice daily until subjects were 2 weeks postpartum. Plasma concentrations of lopinavir were measured over four 12-hour periods during second trimester (20-24 weeks gestation), third trimester before dose increase (30 weeks gestation), third trimester after dose increase (32 weeks gestation), and at 8 weeks postpartum. The dose increase did not result in a significant increase in the plasma lopinavir concentration (See **PREGNANCY AND LACTATION).**

In another open-label pharmacokinetic study, 19 HIV-infected pregnant women received lopinavir/ritonavir 400/100 mg twice daily as part of combination antiretroviral therapy during pregnancy from before conception. A series of blood samples were collected pre-dose and at intervals over the course of 12 hours in trimester 2 and trimester 3, at birth, and 4–6 weeks postpartum (in women who continued treatment post-delivery) for pharmacokinetic analysis of total and unbound levels of plasma lopinavir concentrations (See **PREGNANCY AND LACTATION).**

The pharmacokinetic data from HIV-1 infected pregnant women receiving lopinavir/ritonavir tablets 400/100 mg twice daily are presented in below table:

Mean (%CV) Steady-State Pharmacokinetic Parameters of Lopinavir in HIV-Infected Pregnant Women

Pharmacokinetic Parameter	**2nd Trimester n = 17***	**3rd Trimester n = 23**	**Postpartum n = 17****
AUC_{0-12} µg.hr/mL	68.7 (20.6)	61.3 (22.7)	94.3 (30.3)
C_{max}	7.9 (21.1)	7.5 (18.7)	9.8 (24.3)
$C_{predose}$ µg /mL	4.7 (25.2)	4.3 (39.0)	6.5 (40.4)

*n = 18 for C_{max}

** n = 16 for $C_{predose}$

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 clinically 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.

Pharma - 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 in a 30% increase in lopinavir AUC and 20% 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 (99.09 vs. 99.31% respectively). Lopinavir/ritonavir has not been studied in patients with severe hepatic impairment.

Drug-Drug Interactions

Lopinavir/ritonavir is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of lopinavir/ritonavir and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (See **CONTRAINDICATIONS**).

Lopinavir/ritonavir 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 drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

Lopinavir/ritonavir is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, coadministration of lopinavir/ritonavir and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal silicon dioxide, Sorbitan monolaurate, Copovidone and Sodium Stearyl Fumarate.

Film-coating

Opadry 20C520010 Yellow and Purified water.

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 package. Keep the bottle tightly closed.

6.5 Nature and contents of container

120's Tablets: White opaque 250 cc HDPE bottle closed with 53 mm polypropylene CR Closure with TEKNIPLEX HS 123 induction sealing wad.

The product is intended to be commercialized as cartonless product wherein the pack insert shall be affixed on top of each HDPE bottle. The HDPE bottles shall be bundled and shrink wrapped and placed in the shipper.

6.6 Special precautions for disposal and other handling

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

7. Product Owner

Laurus Labs Limited
2nd Floor, Serene Chambers, Road No.-7
Banjara Hills, Hyderabad – 500034.
India.

Product Registration Holder:
Healol Pharmaceuticals Sdn. Bhd.
74-3, Jalan Wangsa Delima 6,
KLSC Wangsa Maju,
53300 Kuala Lumpur, Malaysia.

Manufacturer:
Laurus Labs Limited, Unit-II
Plot No. 19, 20 & 21, Western Sector, APSEZ,
Gurajapalem Village, Rambilli Mandal,
Anakapalli District-531011, Andhra Pradesh, India.

8. DATE OF REVISION OF THE TEXT

11/2025

2xxxxxx