NEW ZEALAND DATA SHEET

LOPINAVIR/RITONAVIR MYLAN

1. Product Name

Lopinavir/Ritonavir Mylan, 100mg/25mg & 200mg/50mg, film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 100mg/25mg or 200mg/50mg of lopinavir/ritonavir.

Excipients with known effect: Copovidone and sorbitan laurate.

Allergen declaration: sulfites and sorbate.

3. Pharmaceutical Form

100 mg/25 mg: White, film coated, ovaloid, biconvex bevelled edge tablet debossed with 'MLR4' on one side of the tablet and plain on the other side.

200 mg/50 mg: White, film coated, ovaloid, biconvex bevelled edge tablet debossed with 'MLR3' on one side of the tablet and plain on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

Lopinavir/Ritonavir Mylan is indicated for the treatment of HIV-1 infection, in combination with other antiretroviral agents in adults and children aged 2 years and older.

4.2 Dose and method of administration

Dose

Adults

The recommended dosage of Lopinavir/Ritonavir Mylan tablets is 400/100 mg (two 200/50 mg tablets) twice daily. Lopinavir/Ritonavir Mylan tablets may also be administered as 800/200 mg (four 200/50 mg 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 Mylan for adult patients with three or more lopinavir-associated mutations (see section 5.1).

Concomitant Therapy: Efavirenz, Nevirapine, Amprenavir or Nelfinavir

A dose increase of lopinavir/ritonavir to 500/125 mg twice daily (such as two 200/50 mg tablets and one 100/25 mg 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 section 4.5).

Paediatric Patients

The adult dose of Lopinavir/Ritonavir Mylan tablets (400/100 mg twice daily) may be used in children 35 kg or greater. For children weighing less than 35 kg and **able to swallow tablets,** refer to the dosing guideline tables below. Lopinavir/Ritonavir Mylan dosed once daily is not recommended for any paediatric patients.

The following table contains dosing guidelines for Lopinavir/Ritonavir Mylan 100/25 mg tablets in children based on body weight, without efavirenz, nevirapine, nelfinavir or amprenavir.

Table 1: Paediatric Dosing Guidelines

Body Wt (kg)	Recommended number of 100/25 mg Tablets Twice-Daily	Administered Dose
7 < 10	1	100/25 mg
≥ 10 < 25	2	200/50 mg
≥ 25 < 35	3	300/75 mg
≥ 35	4	400/100 mg

Concomitant Therapy: Efavirenz, Nevirapine, Nelfinavir or Amprenavir

The following table contains dosing guidelines for Lopinavir/Ritonavir Mylan 100/25 mg tablets in children based on body weight, when used in combination with efavirenz, nevirapine, nelfinavir or amprenavir.

Table 2: Paediatric Dosing Guidelines with Concomitant Efavirenz, Nevirapine or Amprenavir

Body Wt (kg)	Recommended number of 100/25 mg Tablets Twice-Daily	Administered Dose
≥ 10 to < 20	2	200/50 mg
≥ 20 to < 30	3	300/75 mg
≥ 30 kg to 45 kg	4	400/100 mg
≥ 45 kg	5	500/125 mg

Method of administration

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

4.3 Contraindications

Lopinavir/Ritonavir Mylan is contraindicated in patients with known hypersensitivity to lopinavir, ritonavir, or any excipients (see section 6.1).

Lopinavir/Ritonavir Mylan should not be co-administered concurrently with medicines that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These medicines are listed in Table 3.

Table 3: Medicines which should not be co-administered with lopinavir/ritonavir

Medicine Class	Medicine Within Class Not to Be Co-administered
Alpha1-adrenoreceptor antagonist	Alfuzosin hydrochloride
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, Ergometrine, Methylergometrine
GI motility agent	Cisapride
Herbal product	St Johns 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-adrenoreceptor agonist	Salmeterol
PDE5 inhibitor	Sildenafil* only when used for the treatment of pulmonary arterial hypertension (PAH)
*See section 4.5 co-administration of sildenafil in patients with erectile dysfunction	

4.4 Special warnings and precautions for use

Diabetes Mellitus/Hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia 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 hypoglycaemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycaemia 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 section 4.4*).* 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 metabolised by the liver. Therefore, caution should be exercised when administering this medicine 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 –section 5.2*).* 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 postmarketing 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 section 5.1).

Haemophilia

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. 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.

QT interval prolongation

Post-marketing cases of QT interval prolongation and torsade de pointes have been reported although causality of lopinavir/ritonavir could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalaemia, and with other medicines that prolong the QT interval.

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 pre-existing conduction system abnormalities or in patients receiving medicines 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 (see section 5.2).

Lipid elevations

Treatment with lopinavir/ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides (see section 4.8). 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 section 4.5 for additional information on potential 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, polymyosistis 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.

Paediatric use

The safety, efficacy and pharmacokinetic profiles of lopinavir/ritonavir in paediatric patients below the age of 14 days have not been established. In HIV-infected patients aged 14 days to 18 years, the adverse event profile seen during clinical trials was similar to that for adult patients. Lopinavir/ritonavir should not be administered once daily in paediatric patients.

Use in the elderly

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 therapies.

4.5 Interaction with other medicines and other forms of interaction

Lopinavir/ritonavir is an inhibitor of CYP3A (cytochrome P450 3A) both *in-vitro* and *in-vivo.* Co-administration of lopinavir/ritonavir and medicines primarily metabolised by CYP3A (e.g. dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors) may result in increased plasma concentrations of the other medicines that could increase or prolong their therapeutic and adverse effects. Agents that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when co-administered with lopinavir/ritonavir. Medicines that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in Table 3 under section 4.3 .

Lopinavir/ritonavir is metabolised by CYP3A. Co-administration of lopinavir/ritonavir and medicines that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see section 5.2*).* Although not noted with concurrent ketoconazole, co-administration of lopinavir/ritonavir and other medicines that inhibit CYP3A may increase lopinavir plasma concentrations.

These examples are a guide and not considered a comprehensive list of all possible medicines 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 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 protease inhibitors (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 co-administration. Results from a study in HIV-positive paediatric subjects revealed a decrease in lopinavir concentrations during nevirapine co-administration (see section 5.2). The effect of nevirapine in HIV-positive adults is expected to be similar to that in paediatric 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 should be considered when co-administered with nevirapine (see section 4.2).

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

Efavirenz

Increasing the dose of lopinavir/ritonavir tablets to 500/125 mg (given as two 200/50 mg tablets and one 100/25 mg tablet) twice daily co-administered with efavirenz 600mg once daily resulted in similar lopinavir concentrations compared to lopinavir/ritonavir tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz (see section 4.2).

For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase of lopinavir/ritonavir should be considered when co-administered with efavirenz (see section 4.2).

Increasing the dose of lopinavir/ritonavir tablets to 600/150 mg (three (3) tablets) twice daily 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 twice daily without efavirenz (see section 5.2).

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 twice daily plus lopinavir/ritonavir produces increased AUC, similar C_{max}, increased C_{min}, relative to amprenavir 1200 mg twice daily). Co-administration of lopinavir/ritonavir and amprenavir result in decreased concentrations of lopinavir. The dose of lopinavir/ritonavir may need to be increased when co-administered with amprenavir, particularly in patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir (see section 4.2). 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 twice daily plus lopinavir/ritonavir produces similar AUC, decreased C_{max}, increased C_{min} relative to indinavir 800 mg three times daily). The dose of indinavir may need to be decreased during co-administration with lopinavir/ritonavir 400/100 mg twice daily (see section 5.2). 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 twice daily plus lopinavir/ritonavir produces similar AUC, similar C_{max}, increased C_{min} relative to nelfinavir 1250 mg twice daily). Co-administration of lopinavir/ritonavir and nelfinavir results 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 (see section 4.2). 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 tablets) twice daily (see section 5.2).

Saquinavir

Lopinavir/ritonavir is expected to increase concentrations of saquinavir (saquinavir 800 mg twice daily plus lopinavir/ritonavir produces increased AUC, increased C_{max}, increased C_{min} relative to saquinavir 1200 mg three times daily). The dose of saquinavir may need to be decreased when co-administered with lopinavir/ritonavir 400/100 mg twice daily (see section 5.2). Lopinavir/ritonavir once daily has not been studied in combination with saquinavir.

Tipranavir

In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, tipranavir (500mg twice daily) with ritonavir (200mg twice daily), co-administered with lopinavir/ritonavir (400/100mg 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.

Hepatic C direct acting antivirals

Boceprevir

Concomitant administration of boceprevir and lopinavir/ritonavir resulted in reduced boceprevir and lopinavir steady-state exposure (see section 5.2). 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 increase risk of ALT elevation associated with increased glecaprevir exposure.

Ombitasvir/paritaprevir/ritonavir and dasabuvir

Concentration 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 toxicology, 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 (see section 5.2).

HIV CCR5 - antagonist

Maraviroc

Concurrent administration of maraviroc with lopinavir/ritonavir will increase plasma levels of maraviroc (see section 5.2). The dose of maraviroc should be decreased during co-administration with lopinavir/ritonavir 400/100 mg twice daily. For further details, see complete prescribing information for maraviroc.

Other Medicines

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 section 4.3) systemic lignocaine and quinidine)

Concentrations may be increased when co-administered 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 usually associated with these anticancer agents, some of which may be serious. Co-administration 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, coadministration of apalutamide and lopinavir/ritonavir may lead to increased exposure of apalutamide, resulting in increased potential for adverse events, including seizure.

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.

Anticonvulsants

Phenobarbital, phenytoin, carbamazepine

These medicines are known to induce CYP3A4 and may decrease lopinavir concentrations. Lopinavir/ritonavir should not be administered once daily in combination with carbamazepine, phenobarbital or phenytoin. 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 medicines was associated with reduction in exposure of the anticonvulsant; 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 (see section 5.2).

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 (see section 5.2). High doses of ketoconazole and itraconazole (greater than 200 mg/day) are not recommended.

Voriconazole

Co-administration of voriconazole with lopinavir/ritonavir has not been studied. However, a study has shown that administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of lopinavir/ritonavir and voriconazole may result in decreased voriconazole concentrations and the potential for decreased voriconazole effectiveness and should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Otherwise, alternative antifungal therapies should be considered in these patients.

Antigout Agents

Concentrations of colchicine are expected to increase when co-administered with lopinavir/ritonavir. Life-threatening and fatal medicine interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see section 4.3). Refer to the colchicine product information 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 were increased by 3.5- and 5.7-fold, respectively (see section 5.2). 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.

Rifampicin

Due to large decreases in lopinavir concentrations, rifampicin should not be used in combination with standard dose lopinavir/ritonavir. The use of rifampicin 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 800/200mg lopinavir/ritonavir twice daily resulted in decreases in lopinavir of up to 57%, and co-administration with lopinavir/ritonavir 400/400 mg twice daily resulted in decreases of up to 7% when compared to lopinavir/ritonavir 400/100 mg twice daily dosed in the absence of rifampicin (see section 5.2).

ALT and AST elevations have been noted in studies with 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. The lopinavir/ritonavir dose should then be titrated upwards. Close monitoring of liver function is indicated.

Bedaquiline

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. In a healthy volunteer medicine 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 medicine interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, exposure of delamanid and a delamanid metabolite, DM-6750, were slightly increased. Due to the risk of QTc prolongation associated with exposure to DM-6705, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended.

Anti-parasitic

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

Anti-psychotics

Caution should be exercised when lopinavir/ritonavir is co-administered with quetiapine. Due to CYP3A inhibition of lopinavir/ritonavir, concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities. When quetiapine is administered to patients who are receiving lopinavir/ritonavir, refer to the quetiapine product information for prescribing information.

Corticosteroids

Concomitant use of lopinavir/ritonavir and inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone, 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.

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. Consider alternatives to fluticasone propionate, particularly for long-term use.

Dexamethasone

Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations.

Fluticasone propionate

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.

Dihydropyridines Calcium Channel Blockers

Medicines such as felodipine, nifedipine and nicardipine may have their serum concentrations increased by lopinavir/ritonavir.

PDE5 inhibitors

Particular caution should be used when prescribing avanafil, sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving lopinavir/ritonavir. Co-administration of lopinavir/ritonavir with these medicines is expected to substantially increase their concentrations and may result in increased associated adverse events such as hypotension, and prolonged erection.

Avanafil

Co-administration of lopinavir/ritonavir with avanafil is not recommended, as it is expected to result in large increases in avanafil exposure.

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.

Concomitant use of sildenafil with lopinavir/ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients (see section 4.3).

Tadalafil

Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours, with increased monitoring for adverse events. When tadalafil is administered for the treatment of pulmonary arterial hypertension to patients who are receiving lopinavir/ritonavir, refer to the tadalafil product information 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.

GnRH Receptor antagonists

Elagolix

Coadministration of elagolix with lopinavir/ritonavir could increase elagolix exposure through inhibition of OATP, CYP3A 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 CYP3A4 inhibitors.

Kinase inhibitors (see also cancer 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 protease inhibitors. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance to lopinavir or to the therapeutic class of protease inhibitors (see section 4.3).

HMG-CoA Reductase Inhibitors

Lovastatin and simvastatin

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 medicines with lopinavir/ritonavir is contraindicated (see section 4.3).

Atorvastatin, fluvastatin, pravastatin and rosuvastatin

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.

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.

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 medicine interaction study with lopinavir/ritonavir and pravastatin reveal no clinically significant interaction (see section 5.2).

Microsomal triglyceride transfer protein (MTTP) inhibitor

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 (see section 4.3).

Immunosuppressants

Concentrations of these medicines (e.g. ciclosporin, 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 (see section 5.2).

Oral contraceptives or patch contraceptives

Since levels of ethinyloestradiol may be decreased, alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives or patch contraceptives and lopinavir/ritonavir are co-administered (see section 5.2).

Vasodilating agents

Bosentan

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 product information for prescribing information.

Clinically significant medicine interactions are not expected

Medicine interaction studies reveal no clinically significant interaction with lopinavir/ritonavir administered with desipramine (CYP2D6 probe), omeprazole or ranitidine (see section 5.2).

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

Based on known metabolic profiles, clinically significant medicine 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

Fertility

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at maximum achievable doses producing medicine exposures which were comparable to or slightly less than those achieved with 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 that of the exposures in humans at the recommended therapeutic dose (400/100mg twice daily).

Pregnancy (Category B3)

Risk summary

Lopinavir/ritonavir has been evaluated in 3366 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 aetiology 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 (anaemia 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 pre-eclampsia, 6 preterm deliveries, 7 cases of low birth weight infants (<2,500 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.

No treatment-related malformations were observed when lopinavir/ritonavir was administered to pregnant rats or rabbits. Embryonic and foetal development toxicities (early resorption, decreased foetal viability, decreased foetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50mg/kg/day). Based on AUC measurements, the medicine exposures in rats at 100/50mg/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 (400/100mg twice daily). In a peri- and post-natal study in rats, a developmental toxicity (a decrease in survival of pups between birth and post-natal day 21) occurred at 40/20mg/kg/day and greater.

No embryonic and foetal developmental toxicity was observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the medicine 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 twice daily).

Use in Lactation

Because of the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed when they are receiving Lopinavir/Ritonavir Mylan. Studies in rats showed 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/ritonavir (see section 4.8).

4.8 Undesirable effects

Adults

Treatment-emergent adverse events

The safety of lopinavir/ritonavir has been investigated in over 2600 patients in Phase II-IV clinical trials, of which more than 700 have received a dose of 800/200 mg (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 diarrhoea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. Diarrhoea, 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 (Table 4):

Table 4: 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		
anaemia*	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	0.230
ENDOCRINE DISORDERS		
hypogonadism*	16	0.785[1]
EYE DISORDERS		
visual impairment*	8	0.306
GASTROINTESTINAL DISORDERS		
diarrhoea*	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 (GORD)*	40	1.531
haemorrhoids	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 haemorrhage including rectal haemorrhage*	13	0.498
dry mouth	9	0.345
gastrointestinal ulcer*	6	0.230
faecal 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	3.790
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
haematuria*	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 percentage of adult patients treated with combination therapy including lopinavir/ritonavir with Grade 3 to 4 laboratory abnormalities are presented in Table 5 and 6.

Table 5: 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 mgtwice daily + d4T +3TC (N = 326)**	**Nelfinavir750 mg three times daily + d4T + 3TC (N = 327)**	**Lopinavir/ Ritonavir 800/200 mg once daily + TDF + FTC (N = 115)**	**Lopinavir/ Ritonavir 400/100 mg twice daily + TDF + FTC (N = 75)**	**Lopinavir/ Ritonavir twice daily + d4T + 3TC (N = 100)**	**Lopinavir/ Ritonavir once daily + TDF +FTC (N=333)**	**Lopinavir/ Ritonavir twice daily + 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%
Amylase	> 2 x ULN	3%	2%	7%	5%	4%	N/A	N/A
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%
Haematology	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)

d4T = Stavudine; 3TC = Lamivudine; TDF = Tenofovir; FTC = Emtricitabine

Table 6: 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 400/100 mg twice daily + NVP + NRTIs (N=148)**	**Investigator -selected protease inhibitor(s) + NVP + NRTIs (N=140)**	**Lopinavir/ Ritonavir twice daily + NNRTI + NRTIs (N=127)**	**Lopinavir/ Ritonavir 800/200 mg once daily + NRTIs (N=300)**	**Lopinavir/ Ritonavir 400/100 mg 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/AST[4]	> 180 U/L	5%	11%	8%	3%	2%
SGPT/ALT[4]	> 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	> 2x ULN	N/A	N/A	N/A	4%	1%
Creatine Phosphokinase	> 4x ULN	N/A	N/A	N/A	4%	5%
Chemistry	**Low**					
Calculated Creatinine Clearance	< 50mL/min	N/A	N/A	N/A	3%	3%
Inorganic Phosphorus	< 1.5 mg/dL	1%	0%	2%	1%	<1%
Haematology	Low					
Neutrophils	0.75 x 10^9/L	1%	2%	4%	3%	4%

Haemoglobin	< 80g/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 twice daily (n=29) or 533/133 mg twice daily (n=28) for 84 weeks. Patients received lopinavir/ritonavir in combination with NRTIs and efavirenz.

[3] Includes laboratory data from patients receiving 400/100 mg twice daily (n=36) or 400/200 mg twice daily (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)

NVP = nevirapine

Paediatric population

Treatment-emergent adverse events

Lopinavir/ritonavir has been studied in 100 paediatric 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 diarrhoea were the most commonly reported medicine related adverse events of any severity in paediatric patients treated with combination therapy including lopinavir/ritonavir for up to 48 weeks in study 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 medicine-related clinical adverse event of moderate to severe intensity observed in greater than or equal to 2% of children enrolled.

Laboratory abnormalities

The percentages of paediatric patients aged 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 Table 7.

Table 7: Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% Paediatric Patients

Variable	Limit[+]	Lopinavir/ritonavir twice daily + 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.

Postmarketing experience

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

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

Cardiac disorders: Bradyarrhythmia has been reported.

Renal and urinary disorders: Nephrolithiasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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 medicine should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed medicine. Since lopinavir/ritonavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, antivirals for treatment of HIV infections, combinations, ATC code: J05AR10.

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 (EC50) 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=6). In the presence of 50% human serum, the mean EC50 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 medicine 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 naive paediatric 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 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. Table 8 shows the 48-week virologic response (HIV RNA <400 copies/mL) according to the number of the above protease inhibitor resistance mutations at baseline at studies M98-888 and M97-765 and study M98-957 (see below).

Table 8: 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]

No. of subjects with virologic response / total no. of subjects (%)			
Number of protease inhibitor mutations at baseline[1]	**Single protease inhibitor-experienced[2], NNRTI-naive (n = 130)**	**Single protease inhibitor-experienced[3], NNRTI-naive (n = 56)**	**Multiple protease inhibitor-experienced[4], NNRTI-naive (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, L241, 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.

Table 9 shows the 48-week virologic response (HIV-1 RNA <50 copies/mL) in a study according to the number of lopinavir- associated resistance mutations listed in Table 8 present at baseline (see section 5.1). There are insufficient data to support once daily administration of Lopinavir/Ritonavir Mylan for adult patients with three or more lopinavir-associated mutations.

Table 9: Virologic Response (HIV-1 RNA <50 copies/mL) at Week 48 by Baseline Number of Protease Substitutions Associated with Reduced Response to Lopinavir/Ritonavir[1]		
Number of protease inhibitor mutations at baseline[1]	**Study 802** **(Treatment experienced[2]) Lopinavir/Ritonavir Once Daily + NRTIs (n = 268)**	**Study 802** **(Treatment experienced[3]) Lopinavir/Ritonavir 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 efficacy and safety

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 randomised to receive one of two doses of lopinavir/ritonavir in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC50 values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC50 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.

Clinical efficacy and safety results

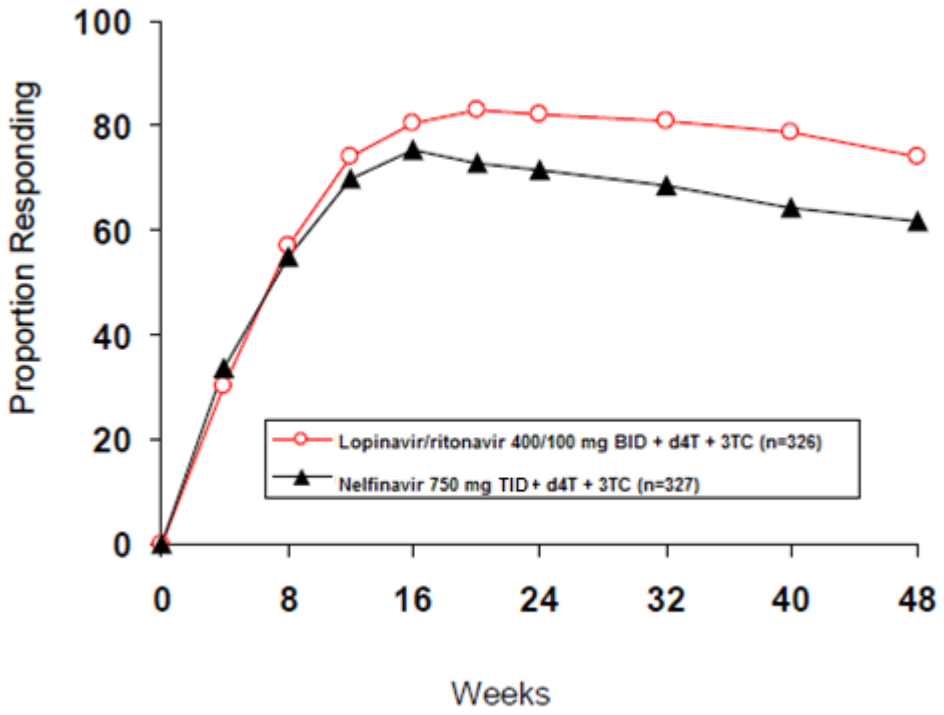
Patients without prior antiretroviral therapy

Study M98-863: Lopinavir/ritonavir capsules twice daily + stavudine + lamivudine compared to nelfinavir three times daily + stavudine + lamivudine.

Study M98-863 was a randomised, double-blind, multicentre trial comparing treatment with lopinavir/ritonavir capsules (400/100 mg twice daily) plus stavudine and lamivudine versus nelfinavir (750 mg three times daily) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4 cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 2.6 to 6.8 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomised treatment are presented in Figure 1 and Table 10, respectively.

Figure 1: Treatment Response Through 48 Weeks* (Study 863)



* Proportion of patients at each time point who have achieved and maintained HIV RNA less than 400 copies/mL, are on their original study medication, and have not experienced a new CDC Class C event.

Table 10: Outcomes of Randomised Treatment Through Week 48 (Study 863)

Outcome	Lopinavir/ritonavir+d4T+3TC (n=326)	Nelfinavir+d4T+3TC (n=327)
Responder*[1]	75%	62%
Virologic failure[2] Rebound Never suppressed through Week 48	9% 7% 2%	25% 15% 9%
Death	2%	1%
Discontinued due to adverse event	4%	4%
Discontinued for other reasons[3]	10%	8%

* Corresponds to rates at Week 48 in Figure 1.

1 Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

2 Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.

3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through week 48, including patients who discontinued subsequent to virologic failure, was 17% in the lopinavir/ritonavir arm and 24% in the nelfinavir arm.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the lopinavir/ritonavir arm compared to the nelfinavir arm with HIV RNA less than 400 copies/mL

(75% vs. 62%, respectively) and HIV RNA less than 50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV RNA level subgroups is presented in Table 11.

Table 11: Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)

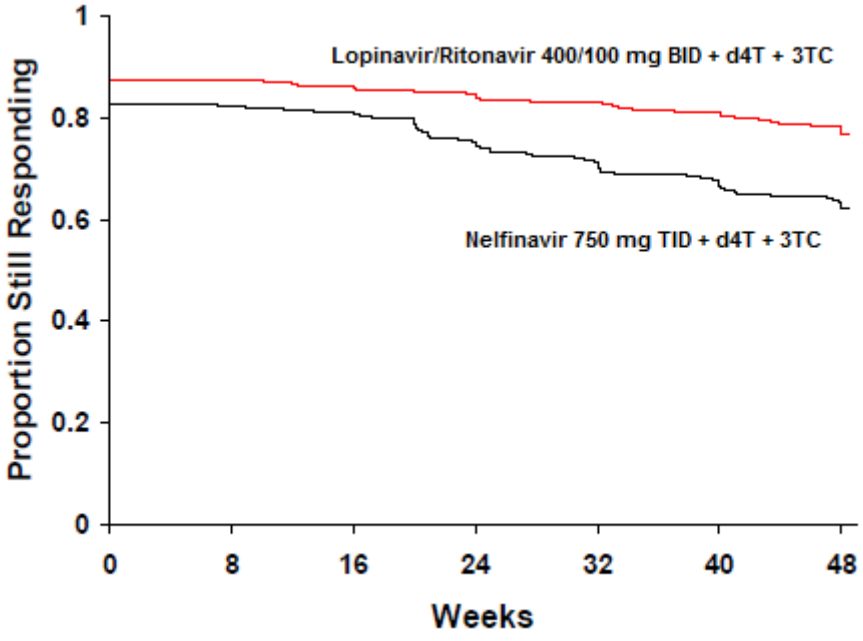
Baseline Viral Load (HIV-1 RNA copies/mL)	Lopinavir/ritonavir +d4T+3TC			Nelfinavir +d4T+3TC		
	<400 copies/mL[1]	<50 copies/mL[2]	n	<400 copies/mL[1]	<50 copies/mL[2]	n
<30,000	74%	71%	82	79%	72%	87
=30,000 to <100,00	81%	73%	79	67%	54%	79
=100,000 to <250,000	75%	64%	83	60%	47%	72
=250,000	72%	60%	82	44%	33%	89

[1] Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.
[2] Patients achieved HIV RNA <50 copies/mL at Week 48.

Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was 207 cells/mm^3 for the lopinavir/ritonavir arm and 195 cells/mm^3 for the nelfinavir arm.

Figure 2 displays the Kaplan-Meier estimates of the time to treatment failure in Study 863. The time of treatment failure was defined as the earliest time a patient experienced virologic failure (two consecutive HIV RNA values demonstrating rebound above 400 copies/mL), a new CDC Class C event, or premature discontinuation from the study.

Figure 2: Time to Treatment Failure (Study 863)



Study M05-730: Lopinavir/ritonavir 800/200mg Once Daily + tenofovir DF + emtricitabine compared to lopinavir/ritonavir 400/100mg twice daily + tenofovir DF + emtricitabine.

Study M05-730 was a randomised, open-label, multicentre trial comparing treatment with lopinavir/ritonavir 800/200 mg once daily plus tenofovir DF and emtricitabine versus lopinavir/ritonavir 400/100 mg twice daily plus tenofovir DF and emtricitabine in 664 antiretroviral treatment-naïve patients. Patients were randomised in a 1:1 ratio to receive either lopinavir/ritonavir 800/200 mg once daily (n = 333) or lopinavir/ritonavir 400/100 mg twice daily (n = 331). Further

stratification within each group was 1:1 (tablet versus soft capsule). Patients were administered either the tablet or the soft capsule formulation for 8 weeks, after which all patients were administered the tablet formulation once daily or twice daily for the remainder of the study. Patients were administered emtricitabine 200 mg once daily and tenofovir DF 300 mg once daily. Mean age of patients enrolled was 39 years (range: 19 to 71); 75% were Caucasian, and 78% were male. Mean baseline CD4+ cell count was 216 cells/mm^3 (range: 20 to 775 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.0 log_{10} copies/mL (range: 1.7 to 7.0 log_{10} copies/mL).

Through 48 weeks of therapy, 78% in the lopinavir/ritonavir once-daily arm and 77% in the lopinavir/ritonavir twice daily arm achieved and maintained HIV-1 RNA < 50 copies/ml (95% confidence interval for the difference: -5.9% to 6.8%). Mean CD4+ cell count increases at Week 48 were 186 cells/mm^3 for the lopinavir/ritonavir once-daily arm and 198 cells/mm^3 for the lopinavir/ritonavir twice-daily arm.

Study M97-720: Lopinavir/ritonavir capsules twice daily + stavudine + lamivudine

Study M97-720 was a randomised, blinded, multicentre trial evaluating treatment with lopinavir/ritonavir capsules at three dose levels (Group I: 200/100 mg twice daily and 400/100 mg twice daily; Group II: 400/100 mg twice daily and 400/200 mg twice daily) plus lamivudine (150 mg twice daily) and stavudine (40 mg twice daily) in 100 patients. All patients were converted to open label lopinavir/ritonavir at the 400/100 mg twice daily dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 70% were Caucasian, and 96% were male. Mean baseline CD4 cell count was 338 cells/mm^3 (range: 3 to 918 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/mL (range: 3.3 to 6.3 log_{10} copies/mL).

Through 360 weeks of treatment in study 720, the proportion of patients with HIV RNA less than 400 (less than 50) copies/mL was 61% (59%) [n=100], and the corresponding mean increase in CD4 cell count was 501 cells/mm^3. Thirty-nine patients (39%) discontinued the study, including 15 (15%) discontinuations due to adverse events and 1 (1%) death. 18 patients demonstrated loss of virologic response (two consecutive rebound HIV-1 RNA values above 400 copies/mL, one rebound HIV-1 RNA value followed by discontinuation, or failure to achieve HIV RNA <400 copies/mL). Genotypic analysis of viral isolates was conducted on these patients and 10 additional patients with isolated HIV-1 RNA values >400 copies/mL after week 24. Results were available from 19 patients and confirmed no primary or active site mutations in protease (amino acids at positions 8, 30, 32, 36, 47, 48, 50, 82, 84 and 90) or protease inhibitor phenotypic resistance.

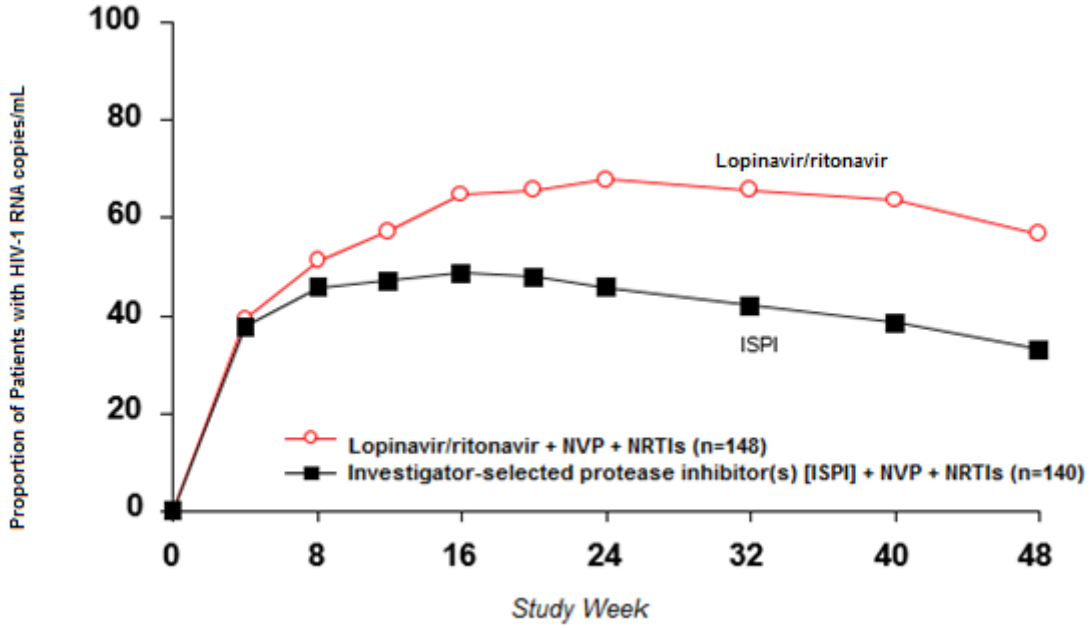
Patients with prior antiretroviral therapy

Study M98-888: Lopinavir/ritonavir capsules twice daily + nevirapine + NRTIs compared to investigator selected protease inhibitor(s) + nevirapine + NRTIs

Study 888 is a randomised, open-label, multicentre trial comparing treatment with lopinavir/ritonavir capsules (400/100 mg twice daily) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naive patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD4 cell count was 322 cells/mm^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 log_{10} copies/mL (range: 2.6 to 6.0 log_{10} copies/mL).

Treatment response and outcomes of randomised treatment through Week 48 are presented in Figure 3 and Table 12 respectively.

Figure 3: Virologic Response Through Week 48, Study 888*†



* Roche AMPLICOR HIV-1 MONITOR Assay.
† Responders at each visit are patients who had achieved and maintained HIV-1 RNA <400 copies/mL without discontinuation by that visit.

Table 12: Outcomes of Randomised Treatment Through Week 48 (Study 888)

Outcome	Lopinavir/ritonavir + nevirapine + NRTIs (n=148)	Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n=140)
Responder*[1]	57%	33%
Virologic Failure[2]	24%	41%
Rebound	11%	19%
Never suppressed through Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons[3]	14%	13%

* Corresponds to rates at Week 48 in Figure 3.
1 Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.
2 Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Study M97-765: Lopinavir/ritonavir capsules twice daily + nevirapine + NRTIs

Study M97-765 was a randomised, blinded, multicentre trial evaluating treatment with lopinavir/ritonavir capsules at two dose levels (400/100 mg twice daily and 400/200 mg twice daily) plus nevirapine (200 mg twice daily) and two NRTIs in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients. Patients had a mean age of 40

years (range 22 to 66), were 73% Caucasian, and were 90% male. Mean baseline CD4 cell count was 372 cells/mm^3 (range: 72 to 807 cells/mm^3) and mean baseline-plasma HIV-1 RNA was 4.0 log_{10} copies/mL (range: 2.9 to 5.8 log_{10} copies/mL).

Through 144 weeks of treatment in study 765, the proportion of patients with HIV RNA less than 400 (less than 50) copies/mL was 54% (50%) [n=70], and the corresponding mean increase in CD4 cell count was 212 cells/mm^3. 27 patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

M06-802: Lopinavir/ritonavir 800/200mg Once Daily + NRTIs compared to lopinavir/ritonavir 400/100mg twice daily + NRTIs in Antiretroviral-Experienced, HIV-1 infected patients.

This study was a randomised open-label study comparing the safety, tolerability, and antiviral activity of once daily and twice daily dosing of lopinavir/ritonavir tablets in 599 subjects with detectable viral loads while receiving their current antiviral therapy. Patients were randomised in a 1:1 ratio to receive either lopinavir/ritonavir 800/200 mg once daily (n = 300) or lopinavir/ritonavir 400/100 mg twice daily (n = 299). Patients were administered at least two nucleoside/nucleotide reverse transcriptase inhibitors selected by the investigator. Mean age of patients enrolled was 41 years (range: 21 to 73); 51% were Caucasian, and 66% were male. Mean baseline CD4+ cell count was 254 cells/mm^3 (range: 4 to 952 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.3 log_{10} copies/mL (range: 1.7 to 6.6 log_{10} copies/mL).

Treatment response and outcomes of randomised treatment through Week 48 are presented in Table 13.

Table 13: Outcomes of Randomised Treatment Through Week 48 (Study 802)

Outcome	Lopinavir/ritonavir Once Daily + NRTIs (n = 300)	Lopinavir/ritonavir Twice Daily + NRTIs (n = 299)
Responder[1]	55%	52%
Virologic failure[2]	25%	28%
Rebound	12%	14%
Never suppressed through Week 48	13%	14%
Death	1%	1%
Discontinued due to adverse events	4%	6%
Discontinued for other reasons[3]	15%	14%

1 Patients achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48.
2 Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48.
3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Paediatric use

Study M98-940

Study M98-940 was an open-label, multicentre trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of lopinavir/ritonavir Oral Solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive (44%) and experienced (56%) paediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomised to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naive patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of five years (range six months to 12 years) with 14% less than two years. Mean baseline CD4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA less than 400 copies/mL was 80% for antiretroviral naive patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm^3 for antiretroviral naive and 284 cells/mm^3 for antiretroviral-experienced patients treated through 48 weeks. Premature discontinuations were noted in 2 (2%) subjects prior to week 48. One of these was considered by the investigator to be "unrelated" to study treatment, the second "possibly" related to study treatment.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine).

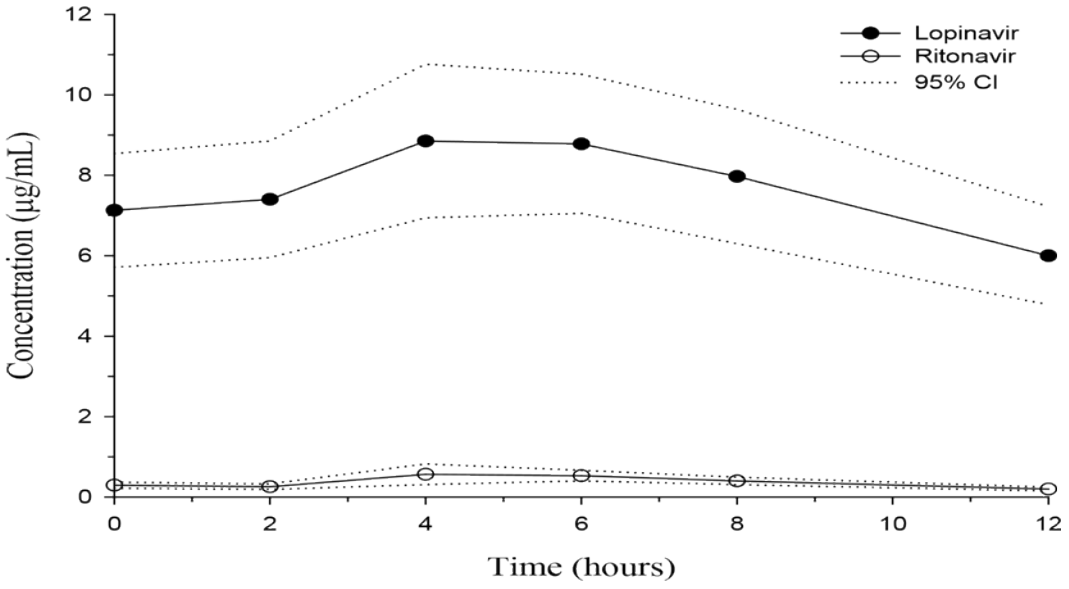
5.2 Pharmacokinetic properties

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 metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir.

Across studies, administration of lopinavir/ritonavir 400/100 mg twice daily yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg twice daily. The *in-vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of lopinavir/ritonavir is due to lopinavir.

Figure 4 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after lopinavir/ritonavir 400/100 mg twice daily with food for three weeks from a pharmacokinetic study in HIV-infected adult subjects (n=19).

Figure 4: Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (n = 19)



Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg tablets are equal to or greater than those obtained with three 133/33 mg tablets under fed conditions with less pharmacokinetic variability.

Absorption

In a pharmacokinetic study in HIV-positive subjects (n=18), multiple dosing with 400/100 mg lopinavir/ritonavir tablets twice daily with or without food for 2 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 12.3 ± 5.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 µg/ml and minimum concentration within a dosing interval was 5.6± 4.5 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 113.2 ± 60.5 µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of food on oral absorption

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.

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 tablets twice daily, and is similar between healthy volunteers and HIV-positive patients.

Biotransformation

In-vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised 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 ^{14}C-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.

Elimination

Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and faeces, respectively, after eight days. Unchanged lopinavir accounted for approximately 2.2% and 19.8% of the administered dose in urine and faeces, 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).

Once daily dosing

The pharmacokinetics of once daily lopinavir/ritonavir tablets have been evaluated in HIV-infected subjects naive 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 peak plasma concentration (C_{max}) of 14.8 ± 3.5 µg/ml, occurring approximately 6 hours after administration. The mean steady-state 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 (see section 4.4).

Special Populations

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.

Paediatric patients

The pharmacokinetics of lopinavir/ritonavir 300/75 mg/m^2 twice daily and 230/57.5 mg/m^2 twice daily have been studied in a total of 53 paediatric patients, ranging in age from six months to 12 years. The 230/57.5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine).

The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1mcg•h/mL, 8.2 ± 2.9 mcg•h/mL and 3.4 ± 2.1 mcg•h/mL, respectively after lopinavir/ritonavir 230/57.5 mg/m^2 twice daily without nevirapine (n=12), and were 85.8 ± 36.9 mcg•h/mL, 10.0 ± 3.3 mcg/mL and 3.6 ± 3.5 mcg/mL, respectively after 300/75 mg/m^2 twice daily with nevirapine (n=12). The nevirapine regimen was 7 mg/kg twice daily (six months to eight years) or 4 mg/kg twice daily (greater than eight years). Lopinavir/ritonavir should not be administered once daily in paediatric patients.

Lopinavir/ritonavir should not be administered once daily in paediatric patients.

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.

Hepatic Impairment

Lopinavir is principally metabolised 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 (see section 4.4).

Medicine Interactions

(See also section 4.3 and 4.5)

Lopinavir/ritonavir is an inhibitor of the P450 isoform CYP3A *in-vitro*. Co-administration of lopinavir/ritonavir and medicines primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicine, which could increase or prolong its therapeutic and adverse effects.

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 medicines metabolised by cytochrome P450 enzymes and by glucuronidation.

Lopinavir/ritonavir is metabolised by CYP3A. Medicines 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, co-administration of lopinavir/ritonavir and other medicines that inhibit CYP3A may increase lopinavir plasma concentrations.

Interaction studies were performed with lopinavir/ritonavir and other medicines likely to be co-administered and some medicines commonly used as probes for pharmacokinetic interactions. The effects of co-administration of lopinavir/ritonavir on the AUC, C_{max} and C_{min} are summarized in Table 14 (effect of other medicines on lopinavir) and Table 15 (effect of lopinavir/ritonavir on other medicines). The effects of other medicines on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see section 4.5.

Table 14. Medicine Interactions
Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Medicine (See section 4.5)

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**Dose of Lopinavir/ Ritonavir (mg)**	**n**	**Ratio (with/without co-administered medicine) of Lopinavir Pharmacokinetic Parameters (90% CI); No effect = 1.00**		
				C_{max}	**AUC**	**C_{min}**
Amprenavir	750 twice daily; 10 days	400/100 capsule twice daily; 21 days	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin	20 Daily; 4 days	400/100 capsule twice daily; 14 days	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Boceprevir	800 eight-hourly; 6 days	400/100 tablet twice daily; 22 days	39	0.70 (0.65, 0.77)	0.66 (0.60, 0.72)	0.57 (0.49, 0.65)

Efavirenz[1]	600 nightly; 9 days	400/100 capsule twice daily; 9 days	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 nightly; 9 days	500/125 tablet twice daily; 10 days	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 nightly; 9 days	600/150 tablet twice daily; 10 days	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Ketoconazole	200 single dose	400/100 capsule twice daily; 16 days	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 twice daily; 10 days	400/100 capsule twice daily; 21 days	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 twice daily, steady-state (>1yr)[2]	400/100 tablet twice daily; steady-state (>1yr)	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
Omeprazole	40 Daily, 5 days	400/100 tablet twice daily; 10 days	11	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)
		800/200 tablet twice daily; 10 days	12	0.94 (0.89, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
Pravastatin	20 Daily; 4 days	400/100 capsule twice daily; 14 days	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Ranitidine	150 single dose	400/100 tablet twice daily; 10 days	12	0.98 (0.95, 1.02)	0.98 (0.94, 1.01)	0.93 (0.89, 0.98)
		800/200 tablet daily; 10 days	11	0.98 (0.95, 1.01)	0.96 (0.90, 1.02)	0.85 (0.67, 1.08)
Rifabutin	150 daily; 10 days	400/100 capsule twice daily; 20 days	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampicin	600 daily; 10 days	400/100 capsule twice daily; 20 days	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 daily; 14 days	800/200 capsule twice daily; 9 days[4]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 daily; 14 days	400/400 capsule twice daily; 9 days[5]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
	Co-administration of standard lopinavir/ritonavir and rifampicin is not recommended (see section 4.4).					

Ritonavir[2]	100 twice daily; 3 to 4 weeks	400/100 capsule twice daily; 3 to 4 weeks	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Telaprevir	750 eight-hourly; 10 days	400/100 twice daily; 20 days	12	0.96 (0.87, 1.05)	1.06 (0.96, 1.17)	1.14 (0.96, 1.36)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.
[2] Study conducted in HIV-positive adult subjects.
[3] Study conducted in HIV-positive paediatric subjects ranging in age from 6 months to 12 years.
[4] Titrated to 800/200 twice daily as 533/133 twice daily x 1 day, 667/167 twice daily x 1 day, then 800/200 twice daily x 7 days, compared to 400/100 twice daily x 10 days alone.
[5] Titrated to 400/400 twice daily as 400/200 twice daily x 1 day, 400/300 twice daily x 1 day, then 400/400 twice daily x 7 days, compared to 400/100 twice daily x 10 days alone.
* Parallel group design; n for lopinavir/ritonavir + co-administered medicine, n for lopinavir/ritonavir alone

Table 15. Medicine Interactions
Pharmacokinetic Parameters for Co-administered Medicine in the Presence of Lopinavir/Ritonavir (See Warnings and Precautions for Recommended Alterations in Dose or Regimen)

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**Dose of Lopinavir/ Ritonavir (mg)**	**n**	**Ratio (with/without Lopinavir/Ritonavir) of Co-administered Medicine Pharmacokinetic Parameters (90% CI); No effect = 1.00**		
				C_{max}	**AUC**	**C_{min}**
Amprenavir[1]	750 twice daily, 10 days combo vs. 1200 twice daily, 14 days	400/100 capsule twice daily, 21 days	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Atorvastatin	20 Daily, 4 days	400/100 capsule twice daily, 14 days	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Boceprevir	800 eight-hourly; 6 days	400/100 tablet twice daily; 22 days	39	0.50 (0.45, 0.55)	0.55 (0.49, 0.61)	0.43 (0.36, 0.53)
Desipramine[2]	100 single dose	400/100 capsule twice daily, 10 days	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	NA
Efavirenz	600 nightly; 9 days	400/100 capsule twice daily, 9 days	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyloestradiol	35 mcg daily; 21 days (Brevinor-1®)	400/100 capsule twice daily, 14 days	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)

Indinavir[1]	600 twice daily, 10 days combo nonfasting vs. 800 three times daily, 5	400/100 capsule twice daily, 15 days	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 capsule twice daily, 16 days	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	NA
Lamotrigine	100 twice daily, 12 days vs 100 twice daily, 8 days	400/100 capsule twice daily; 12 days	18	0.54 (0.49, 0.58)	0.5 (0.47, 0.54)	0.44 (0.40, 0.47)
	200 twice daily, 9 days vs 100 twice daily, 8 days	400/100 capsule twice daily; 9 days	15	1.03 (0.90, 1.17)	0.91 (0.82, 1.02)	0.79 (0.69, 0,90)
Maraviroc	300 twice daily	400/100 capsule twice daily	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)
Methadone	5 single dose	400/100 capsule twice daily, 10 days	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	NA
Nelfinavir[1] M8 metabolite	1000 twice daily, 10 days combo vs. 1250 twice daily, 14 days alone	400/100 capsule twice daily, 21 days	13	0.93 (0.82, 1.05) 2.36 (1.91, 2.91)	1.07 (0.95, 1.19) 3.46 (2.78, 4.31)	1.86 (1.57, 2.22) 7.49 (5.85, 9.58)
Nevirapine	200 daily, 14 days; twice daily, 6 days	400/100 capsule twice daily, 20 days	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethisterone	1 daily, 21 days (Brevinor-1®)	400/100 capsule twice daily, 14 days	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 daily, 4 days	400/100 capsule twice daily, 14 days	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	NA
Rifabutin 25-O-desacetyl rifabutin Rifabutin + 25-O-desacetyl	150 daily 10 days combo vs. 300 daily, 10 days; alone	400/100 capsule twice daily, 10 days	12	2.12 (1.89, 2.38) 23.6 (13.7, 25.3) 3.46 (3.07, 3.91)	3.03 (2.79, 3.30) 47.5 (29.3, 51.8) 5.73 (5.08, 6.46)	4.90 (3.18, 5.76) 94.9 (74.0, 122) 9.53 (7.56, 12.01)

Saquinavir[1]	800 twice daily, 10 days combo vs. 1200 three times daily, 5 days alone, 1200 twice daily, 5 days combo vs. 1200 three times daily, 5	400/100 capsule twice daily, 15 days 400/100 capsule twice daily, 20 days	14 10	6.34 (5.32, 7.55) 6.44 (5.59, 7.41)	9.62 (8.05, 11.49) 9.91 (8.28, 11.86)	16.74 (13.73, 20.42) 16.54 (10.91, 25.08)
Telaprevir	750 eight-hourly, 10 days	400/100 twice daily; 20 days	12	0.47 (0.41, 0.52)	0.46 (0.46, 0.52)	0.48 (0.40, 0.56)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] Ratio of parameters for amprenavir, indinavir, nelfinavir, and saquinavir are not normalized for dose.
[2] Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.
[3] Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.
* Parallel group design; n for lopinavir/ritonavir + co-administered medicine, n for co-administered medicine alone.
NA = not available.

5.3 Preclinical safety data

Acute, subacute and chronic toxicity

Repeat-dose toxicity studies in rodents and dogs identified major target organs as the liver, kidney, thyroid, spleen and circulating red blood cells. Hepatic changes indicated cellular swelling with focal degeneration. While exposure eliciting these changes were comparable to human clinical exposure, dosages in animals were over 6-fold the recommended clinical dose. Mild renal tubular degeneration was confined to mice exposed with at least twice the recommended human exposure; the kidney was unaffected in rats and dogs. Reduced serum thyroxine led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs. Enlarged spleens with histiocytosis were seen in rats but not in other species. Serum cholesterol was elevated in rodents but not in dogs, while triglycerides were elevated only in mice.

Carcinogenicity, mutagenesis and impairment of fertility

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

6. Pharmaceutical Particulars

6.1 List of excipients

Lopinavir/Ritonavir Mylan film coated tablet contains

- Copovidone
- Sorbitan Laurate

- Colloidal anhydrous silica
- Sodium stearylfumarate
- Opadry white

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

HDPE bottle with PP cap and silica gel desiccant. Pack sizes of 60 or 120 film coated tablets.

Cold form OPA/Al/PVC blisters. Pack size of 60 or 120 film coated tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

30 June 2016

10. Date of Revision of the Text

05 December 2023

Summary table of changes

Section	Summary of new information
All	Change “drug” to “medicine”

2	Declaration of allergens.
4.6	Minor editorial changes
4.8	Updated ADR reporting website.
8	Updated sponsor details