SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME (and dosage form)

KALETRA Soft capsules

KALETRA SOLUTION Oral solution

COMPOSITION

KALETRA: Each soft capsule contains 133.3 mg lopinavir and 33.3 mg ritonavir.

Other ingredients include oleic acid, propylene glycol, polyoxyl 35 castor oil, water, gelatine, sorbitol, titanium dioxide, medium chain triglycerides, lecithin, black ink and FD&C Yellow No. 6 (E110).

KALETRA SOLUTION: Each 1 mℓ contains 80 mg lopinavir and 20 mg ritonavir.

Other ingredients include alcohol 42.4 % v/v, high fructose corn syrup, propylene glycol, water, glycerine, povidone, magnasweet-110 flavour, natural & artificial vanilla flavour, polyoxyl 40 hydrogenated castor oil, artificial cotton candy flavour, acesulfame potassium, sodium chloride, sodium citrate, saccharin sodium, citric acid, menthol and peppermint oil.

PHARMACOLOGICAL CLASSIFICATION

A 20.2.8 – Antiviral agents

PHARMACOLOGICAL ACTION

Lopinavir/ritonavir is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. As co-formulated in lopinavir/ritonavir, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.
Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

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*. Reduced viral susceptibility to lopinavir has been observed in clinical studies.

Cross-Resistance

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.

Pharmacokinetics

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 b.i.d. 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 b.i.d. 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.

Absorption

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

Effects of Food on Oral Absorption

Lopinavir/ritonavir co-formulated soft capsules and liquid were bioequivalent under non-fasting conditions (moderate fat meal). Administration of a single 400/100 mg dose of lopinavir/ritonavir soft capsules with a moderate fat meal (500 – 682 kcal, 22.7 to 25.1 % calories from fat) was associated with a mean increase of 48 and 23 % in lopinavir AUC and C_{max}, respectively, relative to fasting. For lopinavir/ritonavir oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54 %, respectively. Relative to fasting, administration of lopinavir/ritonavir with a high fat meal (872 kcal, 55.8 % from fat) increased lopinavir AUC and C_{max} by 97 and 43 %, respectively for soft capsules and 130 and

56 %, respectively for oral solution. To enhance bioavailability and minimise pharmacokinetic variability lopinavir/ritonavir should be taken with 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 is 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 b.i.d., and is similar between healthy volunteers and HIV-positive patients.

Metabolism

In vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively 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. The 4-oxo and 4-hydroxymetabolite epimeric pair are the major metabolites with antiviral activity, but constitute only minute amounts of total plasma radioactivity. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and likely the induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 to 14 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 have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Lopinavir/ritonavir 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once daily regimen. Multiple dosing of

800/200 mg lopinavir/ritonavir once daily for four weeks with food (n = 24) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 11.8 ± 3.7 micrograms/mℓ, occurring approximately six hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 3.2 ± 2.1 micrograms/mℓ and minimum concentration within a dosing interval was 1.7 ± 1.6 micrograms/mℓ. Lopinavir AUC over a 24 hour dosing interval averaged 154.1 ± 61.4 micrograms·h/mℓ.

Effects on Electrocardiogram

Once daily lopinavir/ritonavir may prolong the QTc interval at therapeutic doses. Modest prolongation of the PR interval was noted in subjects receiving lopinavir/ritonavir on Day 3. Maximum PR interval was 286 msec and no second or third degree heart block was observed. (see **SPECIAL PRECAUTIONS**)

Special Populations

Gender, Race and Age

Lopinavir pharmacokinetics have not been studied in elderly patients. No age or 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 b.i.d. and 230/57.5 mg/m^2 b.i.d. 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 b.i.d. regimen without nevirapine and the 300/75 mg/m^2 b.i.d. regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving 400/100 mg b.i.d. regimen (without nevirapine). Lopinavir/ritonavir once daily has not been evaluated in paediatric patients.

The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 micrograms·h/mℓ, 8.2 ± 2.9 and 3.4 ± 2.1 micrograms/mℓ, respectively after lopinavir/ritonavir 230/57.5 mg/m^2 b.i.d. without nevirapine (n = 12), and were 85.8 ± 36.9 micrograms·h/mℓ, 10.0 ± 3.3 and 3.6 ± 3.5 micrograms/mℓ, respectively after 300/75 mg/m^2 b.i.d. with nevirapine (n = 12). The nevirapine regimen was 7 mg/kg b.i.d. (six months to eight years) or 4 mg/kg b.i.d. (greater than eight years).

Renal Insufficiency

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 **PRECAUTIONS**).

INDICATIONS

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection.

CONTRA-INDICATIONS

KALETRA is contra-indicated in patients with known hypersensitivity to lopinavir, ritonavir or any excipients.

KALETRA 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 1.

TABLE 1: Medicines which should not be co-administered with KALETRA

Class of medicine	Medicine within class not to be co-administered
Antipsychotic	Blonanserin
Benzodiazepines	Midazolam, Triazolam
Ergot derivates	Ergotamine, Dihydroergotamine, Ergonovine, Methylergonovine
Neuroleptics	Pimozide
GI motility agent	Cisapride
Antihistamines	Astemizole, Terfenadine
Protease inhibitors	Tipranavir

Herbal Product	St John's Wort *(Hypericum perforatum)*
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin
Long-acting beta-adrenoreceptor agonists	Salmeterol
PDE5 Enzyme Inhibitors	Sildenafil* only when used for the treatment of pulmonary arterial hypertension (PAH)

* See **INTERACTIONS** for co-administration of sildenafil in patients with erectile dysfunction

WARNINGS

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.

Pancreatitis

Pancreatitis, which may be fatal, has been observed in patients taking **KALETRA** therapy, including those who developed marked triglyceride elevations. Although a causal relationship to **KALETRA** has not been established, marked triglyceride elevations increase the risk for development of pancreatitis. However, pancreatitis may develop in the absence of triglyceride elevations. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during **KALETRA** therapy.

Safety and efficacy of **KALETRA** treatment beyond 96 weeks have not been established.

INTERACTIONS

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of **KALETRA** 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 its 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 **KALETRA**. Medicines that are contra-indicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in Table 1 under **CONTRA-INDICATIONS**.

KALETRA is metabolised by CYP3A. Co-administration of **KALETRA** and medicines that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect. Although not noted with concurrent ketoconazole, co-administration of **KALETRA** and other medicines that inhibit CYP3A may increase **KALETRA** plasma concentrations.

Based on known metabolic profiles, clinically significant medicine interactions are not expected between **KALETRA** and desipramine (CYP2D6 probe), fluvastatin, dapsone, trimethoprim/sulfamethoxazole, erythromycin or azithromycin.

ANTI-HIV AGENTS

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Stavudine and Lamivudine

No change in the pharmacokinetics of lopinavir was observed when **KALETRA** was given alone or in combination with stavudine and lamivudine.

Didanosine

It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after **KALETRA** (given with food).

Zidovudine and Abacavir

KALETRA induces glucuronidation, therefore **KALETRA** has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Tenofovir

A study has shown **KALETRA** increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving **KALETRA** and tenofovir should be monitored for tenofovir-associated adverse events.

All

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

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine

No change in the pharmacokinetics of lopinavir was apparent in healthy subjects during nevirapine and **KALETRA** co-administration. Results from a study in HIV-positive paediatric subjects revealed a decrease in lopinavir concentrations during nevirapine co-administration. The effect of nevirapine in HIV-positive adults is expected to be similar to that in paediatric subjects and lopinavir concentrations may be decreased. The clinical significance of the pharmacokinetic interactions is unknown. For patients with

extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase to 533/133 mg b.i.d. **KALETRA** should be considered when co-administered with nevirapine. **KALETRA** should not be administered once daily in combination with nevirapine.

Efavirenz

When used in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in multiple protease inhibitor-experienced subjects, increasing the dose of **KALETRA** 33.3 % from 400/100 mg (three soft capsules) b.i.d. to 533/133 (four soft capsules) b.i.d. yielded similar lopinavir plasma concentrations as compared to historical data of **KALETRA** 400/100 mg b.i.d. For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase to 533/133 mg b.i.d. **KALETRA** should be considered when co-administered with efavirenz. **NOTE:** Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with **KALETRA**. **KALETRA** should not be administered once daily in combination with efavirenz.

Delaviridine

Delaviridine has the potential to increase plasma concentrations of lopinavir.

Protease Inhibitors (PIs)

Ritonavir

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

Amprenavir

KALETRA is expected to increase concentration of amprenavir (amprenavir 750 mg BID plus **KALETRA** produces increased AUC, similar C_{max}, increased C_{min}, relative to amprenavir 1 200 mg BID). Co-administration of **KALETRA** and amprenavir result in decreased concentration of lopinavir. The dose of **KALETRA** may need to be increased during co-administration of amprenavir, particularly in patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir. **KALETRA** should not be administered once daily in combination with amprenavir.

Fosamprenavir

A study has shown that co-administration of **KALETRA** with fosamprenavir lowers amprenavir and lopinavir concentrations. Appropriate doses of the combination of fosamprenavir and **KALETRA** with respect to safety and efficacy have not been established.

Indinavir

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

Nelfinavir

KALETRA is expected to increase concentrations of nelfinavir and increased M8 metabolite of nelfinavir (nelfinavir 1,000 mg BID plus **KALETRA** produces similar AUC, similar C_{max}, increased C_{min} relative to nelfinavir 1,250 mg BID). Co-administration of **KALETRA** and nelfinavir result in decreased concentrations of lopinavir. The dose of **KALETRA** 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. **KALETRA** should not be administered once daily in combination with nelfinavir.

Saquinavir

KALETRA is expected to increase concentrations of saquinavir (saquinavir 800 mg BID plus **KALETRA** produces increased AUC, increased C_{max}, increased C_{min} relative to saquinavir 1 200 mg TID). The dose of saquinavir may need to be decreased when co-administered with **KALETRA** 400/100 mg BID. **KALETRA** 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 (500 mg twice daily) with ritonavir (200 mg twice daily), co-administered with **KALETRA** (400/100 mg twice daily), resulted in a 47 % and 70 % reduction in lopinavir AUC and C_{min} respectively. The concomitant administration of **KALETRA** and tipranavir with low dose ritonavir is therefore not recommended.

OTHER MEDICINES

Antiarrhythmics (amiodarone, bepridil, systemic lidocaine and quinidine)

Concentrations may be increased when co-administered with **KALETRA**. 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.

Anticoagulants

Warfarin concentrations may be affected when co-administered with **KALETRA**. It is recommended that INR (international normalised ratio) be monitored.

Anticonvulsants (phenobarbital, phenytoin, carbamazepine)

These agents are known to induce CYP3A4 and may decrease lopinavir concentrations. **KALETRA** should not be administered once daily in combination with phenobarbital, phenytoin or carbamazepine.

Antidepressants

Bupropion

Concurrent administration of bupropion with **KALETRA** 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.

Antiparasitic

Atovaquone

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

Corticosteroid

Dexamethasone

Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations.

Fluticasone propionate

Concomitant use of fluticasone propionate and **KALETRA** (lopinavir/ritonavir) may increase concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.

Dihydropyridine Calcium Channel Blockers (e.g. felodipine, nifedipine, nicardipine)

May have their serum concentration increased by **KALETRA**.

Disulfiram/Metronidazole

KALETRA SOLUTION contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other medicines producing this reaction, such as metronidazole.

HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with **KALETRA**. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with **KALETRA** is contra-indicated (see **CONTRA-INDICATIONS**). Atorvastatin is less dependant on CYP3A for metabolism. When atorvastatin was given concurrently with **KALETRA**, a mean 4.7-fold and 5.9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with **KALETRA**, the lowest possible doses of atorvastatin should be administered. Results from an interaction study with **KALETRA** and pravastatin revealed no clinically significant interaction. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with **KALETRA**. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

In a pharmacokinetic study, co-administration of rosuvastatin and a combination product of 400 mg lopinavir / 100 mg ritonavir in healthy volunteers was associated with an approximately two-fold and five-fold increase in rosuvastatin steady-state $AUC_{(0-24)}$ and C_{max} respectively. The lowest dose of rosuvastatin that provides therapeutic benefit to the patient should be used. When initiating and up-titrating rosuvastatin treatment in HIV-infected patients receiving **KALETRA**, consideration should be

given to both the benefit of the lipid lowering effect of rosuvastatin and the potential risks of increased rosuvastatin levels, since the combination may lead to an increased incidence of adverse events.

Immunosuppressants

Concentrations of these agents (e.g. cyclosporin, tacrolimus and sirolimus [rapamycin]) may be increased when co-administered with **KALETRA**. More frequent therapeutic concentration monitoring is recommended until blood levels of these products have stabilised.

Antifungals

Ketoconazole and Itraconazole

Ketoconazole and itraconazole may have serum concentrations increased by **KALETRA**. High doses of ketoconazole and itraconazole (greater than 200 mg/day) are not recommended.

Voriconazole

A study has shown that co-administration of ritonavir 300 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82 %; therefore, co-administration of lopinavir/ritonavir and voriconazole is not recommended.

Anti-infective

Clarithromycin

Moderate increases in clarithromycin AUC are expected when co-administered with **KALETRA**. For patients with renal and hepatic impairment dose reduction of clarithromycin should be considered.

Methadone

KALETRA was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Oral Contraceptives or patch contraceptive

Since levels of ethinyl oestradiol may be decreased, alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives or patch contraceptives and **KALETRA** are co-administered.

Anti-mycobacterial

Rifabutin

When rifabutin and **KALETRA** were co-administered for 10 days, rifabutin (parent drug and active 25-*O*-desacetyl metabolite) C_{max} and AUC were increased by 3.5- and 5.7-fold, respectively. On the basis of these data, a rifabutin dose reduction of 75 % (i.e. 150 mg every other day or 3 times per week) is recommended when administered with **KALETRA**. Further dose reduction of rifabutin may be necessary.

Rifampicin

Due to large decreases in lopinavir concentrations, rifampin should not be used in combination with **KALETRA.** The use of rifampin with **KALETRA**, may lead to loss of virologic response and possible resistance to **KALETRA** or to the class of protease inhibitors or other co-administered antiretroviral agents. A study evaluated combination of rifampin 600 mg QID, with **KALETRA** 800/200 mg BID or **KALETRA** 400/100 mg plus ritonavir 300 mg BID. Pharmacokinetic and safety results from this study do not allow for a dose recommendation. Nine subjects (28 %) experienced a greater than or equal to grade 2 increase in ALT/AST, of which seven (21 %) prematurely discontinued study per protocol. Based on the study design, it is not possible to determine whether the frequency or magnitude of the ALT/AST elevations observed is higher than what would be seen with rifampin alone.

Erectile Dysfunction Agents (PDE5 Inhibitors)

Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving **KALETRA**. Co-administration of **KALETRA** with these medicines is expected to substantially increase their concentrations and may result in increased associated adverse events such as hypotension, syncope, visual changes and prolonged erection. Concomitant use of sildenafil with **KALETRA** is contra-indicated in pulmonary arterial hypertension (PAH) patients. (see **CONTRA-INDICATIONS**)

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 **KALETRA** is contra-indicated in pulmonary arterial hypertension (PAH) patients (see **CONTRA-INDICATIONS**)

Tadalafil

Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events.

Vardenafil

Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.

Herbal Products

St John's Wort (Hypericum perforatum)

Patients on **KALETRA** should not use products containing St John's Wort because co-administration may be expected to reduce plasma concentrations of protease inhibitors. This effect may be due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance to lopinavir or to the therapeutic class of protease inhibitors. (See **CONTRA-INDICATIONS**)

PREGNANCY AND LACTATION

The safety of this medicine in pregnant women has not been established, as there are no adequate and well-controlled studies in pregnant women. **KALETRA** should be used during pregnancy only if the potential benefits clearly outweigh the potential risks.

HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving **KALETRA**. It is not known whether lopinavir is secreted in human milk.

DOSAGE AND DIRECTIONS FOR USE

Adults

KALETRA capsules and oral solution must be taken with food.

The recommended oral dose of **KALETRA** is as follows:

Therapy-Naïve Patients

⇨ **KALETRA** 400/100 mg (three [**3**] soft capsules or **5.0** mℓ) **twice** daily taken with food

⇨ **KALETRA** 800/200 mg (six [**6**] soft capsules or **10.0** mℓ) **once** daily taken with food

Therapy-Experienced Patients

⇨ **KALETRA** 400/100 mg (three [**3**] soft capsules or **5.0** mℓ) **twice** daily taken with food

Once daily administration of **KALETRA** has not been studied in therapy experienced patients and therefore, is not recommended.

Concomitant Therapy

Omeprazole and Ranitidine

KALETRA soft capsules and **KALETRA SOLUTION** can be used in combination with acid reducing agents (omeprazole and ranitidine) with no dose adjustment.

Efavirenz, Nevirapine, Amprenavir or Nelfinavir

A dose increase of **KALETRA** to 533/133 mg (four capsules or 6.5 mℓ) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine, amprenavir or nelfinavir in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). See **INTERACTIONS**.

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

Paediatric Patients

In children 6 months to 12 years of age, the recommended dosage of **KALETRA SOLUTION** is 12.0/3.0 mg/kg for those 7 to less than 15 kg and 10.0/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice daily taken with food, up to a maximum dose of 400/100 mg in children greater than 40 kg (5.0 mℓ or three capsules) twice daily. **KALETRA** once-daily has not been evaluated in paediatric patients. It is preferred that the prescriber calculate the approximate milligram dose for each individual child less than or equal to 12 years old and determine the corresponding volume of solution or number of capsules. Alternatively, the following table contains dosing guidelines for **KALETRA SOLUTION** based on body weight.

TABLE 2: Dosing guidelines for KALETRA SOLUTION without nevirapine, efavirenz, amprenavir or nelfinavir

WEIGHT (kg)	**DOSE (mg/kg)** *	**VOLUME OF ORAL SOLUTION BID (80 mg lopinavir/20 mg ritonavir per mℓ)**
7 to less than 15 kg	**12 mg/kg BID**	
7 to 10 kg		1.25 mℓ

Greater than 10 to less than 15 kg		1.75 mℓ
15 to 40 kg	**10 mg/kg BID**	
15 to 20 kg		2.25 mℓ
Greater than 20 to 25 kg		2.75 mℓ
Greater than 25 to 30 kg		3.50 mℓ
Greater than 30 to 35 kg		4.00 mℓ
Greater than 35 to 40 kg		4.75 mℓ
Greater than 40 kg	**Adult dose**	5.00 mℓ (or three capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mℓ).

Note: Use adult dosage recommendation for children older than 12 years of age.

Concomitant Therapy

Efavirenz, Nevirapine, Amprenavir or Nelfinavir

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

TABLE 3: Dosing guidelines for KALETRA SOLUTION with efavirenz, nevirapine, amprenavir or nelfinavir.

WEIGHT (kg)	**DOSE (mg/kg) ***	**VOLUME OF ORAL SOLUTION BID (80 mg lopinavir/20 mg ritonavir per mℓ)**
7 to less than 15 kg	**13 mg/kg BID**	
7 to 10 kg		1.50 mℓ
Greater than 10 to less than 15 kg		2.00 mℓ
15 to 40 kg	**11 mg/kg BID**	
15 to 20 kg		2.50 mℓ
Greater than 20 to 25 kg		3.25 mℓ
Greater than 25 to 30 kg		4.00 mℓ
Greater than 30 to 35 kg		4.50 mℓ
Greater than 35 to 40 kg		4.75 mℓ (or three capsules)
Greater than 40 to 45 kg		5.75 mℓ
Greater than 45 kg	**Adult dose**	6.50 mℓ (or four capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mℓ).

Note: Use adult dosage recommendation for children older than 12 years of age.

Dosing Guidelines using Body Surface Area (BSA) (m^2)

Oral Solution

Paediatric use (6 months of age and above): The recommended dosage of **KALETRA SOLUTION** is 230/57.5 mg/m^2 twice daily taken with food, up to a maximum dose of 400/100 mg (5.0 mℓ) twice daily.

The 230/57.5 mg/m^2 dosage might be insufficient in some children when co-administered with nevirapine, efavirenz, nelfinavir or amprenavir. An increase in the dose of **KALETRA** to 300/75 mg/m^2 should be considered in these patients. Dose should be administered using a calibrated oral dosing syringe.

Capsules

Paediatric use (6 months of age and above): The recommended dosage of **KALETRA** for children with a Body Surface Area of 1.3 m^2 or greater, is three capsules twice daily taken with food. For children with a Body Surface Area of less than 1.3 m^2, use of **KALETRA SOLUTION** is recommended.

TABLE 4: KALETRA SOLUTION Paediatric Dosing Guidelines

BODY SURFACE AREA (m^2)*	TWICE DAILY DOSAGE (230/57.5 mg/m^2)
0.25	0.7 mℓ (57.5/14.4 mg)
0.50	1.4 mℓ (115/28.8 mg)
0.75	2.2 mℓ (172.5/43.1 mg)
1.00	2.9 mℓ (230/57.5 mg)
1.25	3.6 mℓ (287.5/71.9 mg)
1.50	4.3 mℓ (345/86.3 mg)
1.75	5.0 mℓ (402.5/100.6 mg)

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS

The most frequent adverse event associated with **KALETRA** therapy was diarrhoea, which was of mild to moderate severity. The incidence of diarrhoea was greater for **KALETRA** capsules once-daily compared to **KALETRA** capsules twice daily.

Adults

Treatment-Emergent Adverse Events

The following adverse reactions of moderate to severe intensity with possible or probable relationship to **KALETRA** have been reported. The adverse reactions are displayed by system organ class. Within the system organ class adverse reactions are listed by frequency, using the following groupings: very common >1/10; common >1/100, <1/10 and uncommon >1/1,000, <1/100.

Undesirable Effects in Clinical Studies in Adult Patients

Undesirable Effects in Clinical Studies in Adult Patients		
Infections and infestations	Uncommon	Otitis media, bronchitis, sinusitis, furunculosis, bacterial infection, viral infection, pharyngitis, flu syndrome, gastroenteritis, sialadenitis
Neoplasms benign, malignant and unspecified	Uncommon	Skin benign neoplasm, cyst, neoplasm
Blood and lymphatic system disorders	Uncommon	Anaemia, leucopenia, lymphadenopathy
Immune system disorders	Uncommon	Allergic reactions
Endocrine disorders	Uncommon	Hypogonadism male, Cushing syndrome, hypothyroidism
Metabolic and nutritional disorders	Uncommon	Avitaminosis, dehydration, increased appetite, lactic acidosis, obesity, anorexia, diabetes mellitus, weight gain, weight loss
Psychiatric disorders	Uncommon	Abnormal dreams, agitation, anxiety, confusion, depression, emotional lability, decreased libido, nervousness, abnormal thinking, apathy
Nervous System disorders	Common Uncommon	Headache, insomnia Dizziness, amnesia, ataxia, encephalopathy, facial paralysis, hypertonia, neuropathy, paraesthesia, peripheral neuritis, somnolence, tremor, taste loss, taste perversion, migraine, dyskinesia, cerebral infarct, convulsion, extrapyramidal syndrome
Eye disorders	Uncommon	Abnormal vision, eye disorder
Ear and labyrinth disorders	Uncommon	Tinnitus, vertigo
Cardiac disorders	Uncommon	Palpitation, arterial fibrillation, myocardial infarct
Vascular disorders	Uncommon	Hypertension, thrombophlebitis, vasculitis, varicose vein, deep thrombophlebitis, vascular disorder, postural hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, rhinitis, asthma, lung oedema, cough increased
Gastrointestinal disorders	Very common	Diarrhoea

Undesirable Effects in Clinical Studies in Adult Patients		
	Common Uncommon	Nausea, vomiting, abdominal pain, abnormal stools, dyspepsia, flatulence Abdomen enlarged, constipation, dry mouth, dysphagia, enterocolitis, eructation, enteritis, oesophagitis, faecal incontinence, gastritis, haemorrhagic colitis, mouth ulcerations, pancreatitis, stomatitis, ulcerative stomatitis, periodonitis
Hepatobiliary disorders	Uncommon	Cholecystitis, hepatitis, cholangitis, jaundice, hepatomegaly, liver fatty deposit, liver tenderness
Skin and subcutaneous disorders	Common Uncommon	Rash, lipodystrophy Alopecia, dry skin, eczema, exfoliative dermatitis, maculopapular rash, nail disorder, pruritis, seborrhoea, skin discolouration, skin ulcer, face oedema, acne, sweating, skin striae
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, arthrosis, myalgia, back pain, bone necrosis, joint disorder, myasthenia
Renal and urinary disorders	Uncommon	Kidney calculus, urine abnormality, nephritis
Reproductive system and breast disorders	Uncommon	Abnormal ejaculation, breast enlargement, gynaecomastia, impotence
General disorders and administration site conditions	Common Uncommon	Asthenia Chest pain, chest pain substernal, chills, fever, malaise, pain, peripheral oedema, medicine interaction, oedema, hypertrophy

Paediatric

Treatment-Emergent Adverse Events

Rash (2 %) was the only medicine-related clinical adverse event of moderate or severe intensity in greater than or equal to 2 % of paediatric patients treated with combination therapy including **KALETRA** (300/75 mg/m^2) for up to 24 weeks (Study M98-940). This includes adverse events of at least possible, probable or unknown relationship to study medicine.

Laboratory Abnormalities

The percentage of adult patients treated with combination therapy including **KALETRA** with Grade 3 to 4 laboratory abnormalities are presented in **TABLE 5** and **TABLE 6.**

TABLE 5: GRADE 3-4 LABORATORY ABNORMALITIES REPORTED IN ≥ 2 % OF ADULT ANTIRETROVIRAL- NAÏVE PATIENTS

		Study M98-863 (48 weeks)		Study M02-418 (48 weeks)		Study M97-720 (204 weeks)
Variable	Limit	**KALETRA** 400/100 mg BID + d4T + 3TC (n = 326)	Nelfinavir 750 mg TID + d4T + 3TC (n = 327)	**KALETRA** 800/200 mg QD + TDF + FTC (n = 115)	**KALETRA** 400/100 mg BID + TDF + FTC (n=75)	**KALETRA** BID+ d4T+ 3TC (n = 100)
Chemistry	**High**					
Glucose	> 13.8 mmol/ℓ	2 %	2 %	3 %	1 %	4 %
Uric Acid	> 0.71 mmol/ℓ	2 %	2 %	0 %	3 %	3 %
SGOT/AST	> 180 U/ℓ	2 %	4 %	5 %	3 %	9 %
SGPT/ALT	> 215 U/ℓ	4 %	4 %	4 %	3 %	9 %
GGT	> 300 U/ℓ	N/A	N/A	N/A	N/A	6 %
Total cholesterol	> 7.77 mmol/ℓ	9 %	5 %	3 %	3 %	22 %
Triglycerides	> 8.25 mmol/ℓ	9 %	1 %	5 %	4 %	22 %
Amylase	> 2[1] ULN	3 %	2 %	7 %	5 %	4 %
Haematology	**Low**					
Neutrophils	0.75 x 10^9/ℓ	1 %	3 %	5 %	1 %	5 %

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

TABLE 6: GRADE 3 – 4 LABORATORY ABNORMALITIES REPORTED IN ≥ 2 % OF ADULT PROTEASE INHIBITOR-EXPERIENCED PATIENTS

		Study M98-888 (48 weeks)		Study 957[2] & Study M97-765[3] (84-144 weeks)
Variable	Limit	**KALETRA** 400/100 mg BID + NVP + NRTIs (n = 148)	Investigator-selected protease inhibitor(s) + NVP + NRTIs (n = 140)	**KALETRA** BID + NNRTI + NRTIs (n = 127)
Chemistry	**High**			
Glucose	> 13.8 mmol/ℓ	1 %	2 %	5 %
Total bilirubin	> 59.5 mcmol/ℓ	1 %	3 %	1 %

		Study M98-888 (48 weeks)		Study 957[2] & Study M97-765[3] (84-144 weeks)
Variable	Limit	**KALETRA** 400/100 mg BID + NVP + NRTIs (n = 148)	Investigator-selected protease inhibitor(s) + NVP + NRTIs (n = 140)	**KALETRA** BID + NNRTI + NRTIs (n = 127)
SGOT/AST	> 180 U/ℓ	5 %	11 %	8 %
SGPT/ALT	> 215 U/ℓ	6 %	13 %	10 %
GGT	> 300 U/ℓ	N/A	N/A	29 %
Total cholesterol	> 7.77 mmol/ℓ	20 %	21 %	39 %
Triglycerides	> 8.25 mmol/ℓ	25 %	21 %	36 %
Amylase	> 2[1] ULN	4 %	8 %	8 %
Chemistry	**Low**			
Inorganic Phosphorous	< 0.48 mmol/ℓ	1 %	0 %	2 %
Haematology	**Low**			
Neutrophils	0.75 x 10^9/ℓ	1 %	2 %	4 %

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

[2] Includes clinical laboratory data from patients receiving 400/100 mg BID (n = 29) or 533/133 mg BID (n = 28) for 84 weeks. Patients received **KALETRA** in combination with NRTIs and Efavirenz.

[3] Includes clinical laboratory data from patients receiving 400/100 mg BID (n = 36) or 400/200 mg BID (n = 34) for 144 weeks. Patients received **KALETRA** in combination with NRTIs and Nevirapine.

TABLE 7: Laboratory Abnormalities Reported in ≥ 2 % Paediatric Patients

Variable	Limit [1]	Kaletra BID[2] + RTIs (n = 100)
Chemistry	**High**	
Total bilirubin	> 2.9 x ULN	3.0 %
SGOT/AST	> 180 x U/ℓ	7.0 %
SGPT/ALT	> 215 x U/ℓ	4.0 %
Total cholesterol	> 7.77 mmol/ℓ	2.0 %
Amylase	> 2.5 x ULN	4.0 %
Chemistry	**Low**	
Sodium	< 130 mmol/ℓ	3.0 %
Haematology	**Low**	
Platelet Count	< 50 x 10^9/ℓ	4.0 %
Neutrophils	<0.40 x 10^9/ℓ	2.0 %

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

[2] Includes clinical laboratory data from the 230/57.5 mg per m^2 (n = 49) and 300/75 mg per m^2 (n = 51) dose arms.

Postmarketing Experience

Hepatitis has been reported in patients on **KALETRA** therapy.

Stevens Johnson Syndrome and erythema multiforme have been reported.

Bradyarrhythmia has been reported.

SPECIAL PRECAUTIONS

Hepatic Impairment

KALETRA is principally metabolised by the liver. Therefore, caution should be exercised when administering this medicine to patients with impaired hepatic function. **KALETRA** 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. 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 post-marketing reports of hepatic dysfunctions, 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 **KALETRA** therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of **KALETRA** treatment.

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of **KALETRA** therapy on the efficacy of subsequently administered protease inhibitors is under investigation.

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.

PR Interval Prolongation

KALETRA has been shown to cause prolongation of the PR interval in some patients. Reports of second or third degree atrioventricular block occurred mostly in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicines known to also

prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving **KALETRA**. **KALETRA** should be used with caution in such patients.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations

Treatment with **KALETRA** has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating **KALETRA** therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **INTERACTIONS** for additional information on potential drug interactions with **KALETRA** and HMG CoA reductase inhibitors.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including **KALETRA**. 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.

Information for Patients

Patients should remain under the care of a physician while using **KALETRA**. Patients should be advised to take **KALETRA** and other concomitant antiretroviral therapy every day as prescribed. **KALETRA** must always be used in combination with other antiretroviral medicines. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of **KALETRA** is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that **KALETRA** is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of **KALETRA** are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with **KALETRA** can reduce the risk of transmitting HIV to others through sexual contact.

KALETRA may interact with some medicines; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's Wort.

Patients taking didanosine should take didanosine one hour before or two hours after **KALETRA**.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes and sustained erection and should promptly report any symptoms to their doctor.

Patients receiving oestrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with **KALETRA**. **KALETRA** should be taken with food to enhance absorption. Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Carcinogenesis and Mutagenesis

Long-term carcinogenicity studies of **KALETRA** in animal systems have not been completed. Lopinavir was not found to be mutagenic or clastogenic.

Geriatric Use

Caution should be exercised in the administration and monitoring of **KALETRA** in elderly patients reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other medicine therapy.

Paediatric Use

The safety and pharmacokinetic profiles of **KALETRA** in paediatric patients below the age of six months have not been established. In HIV-infected patients age six months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Treatment of overdose with **KALETRA** 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 **KALETRA**. 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 **KALETRA** is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

KALETRA SOLUTION contains 42.4 % (v/v) alcohol. Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity.

IDENTIFICATION

KALETRA: Oblong orange capsules printed in black ink with the "Abbott Logo" and "PK" containing a clear liquid essentially free of particles.

KALETRA SOLUTION: A light yellow to golden clear liquid, essentially free of particles, supplied in amber-coloured multiple-dose bottles.

PRESENTATION

KALETRA: The soft capsules are supplied in high-density polyethylene (HDPE) bottles closed with polypropylene caps containing 90 capsules. Each pack contains two bottles (180 capsules). **KALETRA** soft capsules are also supplied in blisters. Each carton contains five foil blisters each containing six capsules (30 capsules). Each pack contains six cartons (180 capsules).

KALETRA SOLUTION: The oral solution is supplied in amber coloured multiple-dose polyethylene terephthalate (PET) bottles in a 60 mℓ size. Each pack contains five bottles of 60 mℓ (300 mℓ). Five 5ml syringes (5ml ≈ 400/100 mg dose) are provided.

STORAGE INSTRUCTIONS

Store **KALETRA** soft capsules in a refrigerator at 2 to 8 ºC until dispensed. Refrigeration of **KALETRA** soft capsules is not required by the patient if used within 42 days and stored below 25 ºC.

Store **KALETRA SOLUTION** in a refrigerator at 2 to 8 ºC until dispensed. Refrigeration of **KALETRA SOLUTION** by the patients is not required if used within 42 days and stored below 25 ºC. Keep well closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

KALETRA : 35/20.2.8/0254

KALETRA SOLUTION : 35/20.2.8/0255

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AbbVie (Pty) Limited

Abbott Place, 219 Golf Club Terrace

Constantia Kloof, 1709

REPUBLIC OF SOUTH AFRICA

DATE OF PUBLICATION OF THE PACKAGE INSERT

28 August 2010