## PROFESSIONAL INFORMATION

**SCHEDULING STATUS**

Schedule 4

## 1 NAME OF THE MEDICINE

**KALETRA** (80 mg / 20mg) / ml Oral Solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Each 1 ml contains 356,3 mg of alcohol (42,4 % v/v), 168,6 mg of high fructose corn syrup, 152,7 mg of propylene glycol (15,3 % w/v) (see section 4,3), 10,2 mg of polyoxyl 40 hydrogenated castor oil and 4,1 mg of acesulfame potassium (see section 4,4).

For the full list of excipients, see section 6,1.

## 3. PHARMACEUTICAL FORM

KALETRA SOLUTION: Oral Solution

A light yellow to golden clear liquid, essentially free of particles.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

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

## 4.2. Posology and method of administration

### Posology

*KALETRA should be initiated by medical practitioners who are experienced in the treatment of HIV infection.*

*Adults*

The recommended oral dose of KALETRA is as follows:

KALETRA 400/100 mg (**5,0** mL) **twice** daily taken with food

KALETRA 800/200 mg (**10,0** mL) **once** daily taken with food, in patients with less than three lopinavir-associated mutations. There are insufficient data to support the use of once daily administration of KALETRA for adult patients with three or more lopinavir-associated mutations.

KALETRA should not be administered once daily in combination with carbamazepine, Phenobarbitone or phenytoin (see section 4,5).

***Concomitant Therapy***

*Omeprazole and Ranitidine*

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

*Efavirenz, Nevirapine, Amprenavir or Nelfinavir*

A dose increase of KALETRA to 533/133 mg (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 section 4,5.

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

***Paediatric patients***

Total amounts of alcohol and propylene glycol from all medicines, including KALETRA SOLUTION, that are to be given to infants should be taken into account in order to avoid toxicity from these excipients (see sections 2, 4,4 and 4,9).

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) twice daily. KALETRA should not be administered once-daily 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. Alternatively, the following table contains dosing guidelines for KALETRA SOLUTION based on body weight.

**TABLE 1: 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 |

* 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 2: 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 |
| Greater than 40 to 45 kg | | 5,75 mL |
| | | |
| **Greater than 45 kg** | **Adult dose** | 6,50 mL |

* 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.

**TABLE 3: 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

**Method of administration**

KALETRA is administered orally and should always be taken with food (see section 5,2).

## 4.3 Contraindications

KALETRA is contra-indicated in patients with known hypersensitivity to lopinavir, ritonavir or any excipients listed in section 6,1.

**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 4.

**TABLE 4: Medicines which should not be co-administered with KALETRA**

| **Class of medicine** | **Medicine within class not to be co-administered** |
|---|---|
| Alpha1-adrenoreceptor antagonists | Alfuzosin HCl |
| Antianginal | Ranolazine |
| Antidysrhythmic | Amiodarone, Dronedarone |
| Antibiotics | Fusidic acid |
| Anticancer Agents | Neratinib, apalutamide |
| Antigout | Colchicine in patients with renal and/or hepatic impairment |
| Antihistamines | Astemizole, Terfenadine |
| Antipsychotics | Blonanserin, Lurasidone, Quetiapine, Pimozide |
| Benzodiazepines | Midazolam, Triazolam |
| Ergot derivates | Ergotamine, Dihydroergotamine, Ergonovine, Methylergonovine |
| GI motility medicine | Cisapride |
| Herbal Product | St John's Wort *(Hypericum perforatum)* |
| Hepatitis C virus direct acting antivirals | Elbasvir/grazoprevir |
| Lipid-modifying agents | |
| HMG-CoA Reductase Inhibitors | Lovastatin, simvastatin |
| | Lomitapide |

| | |
|---|---|
| Microsomal triglyceride transfer protein (MTTP) inhibitor | |
| Long-acting beta-adrenoreceptor agonists | Salmeterol |
| PDE5 Enzyme Inhibitors | Sildenafil* only when used for the treatment of pulmonary arterial hypertension (PAH) |
| | Avanafil, Vardenafil (see sections 4,4 and 4,5) |

* See section 4,5 for co-administration of sildenafil in patients with erectile dysfunction

**4.4 Special warnings and precautions for use**

***Antigout medicines***

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 and 4,5).

***Anti-mycobacterial***

Standard dose KALETRA should not be co-administered with rifampin because large decreases in lopinavir concentrations may significantly decrease the therapeutic effect (see section 4,5).

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 (see section 4,5). Bedaquiline must be used cautiously with **KALETRA**, only if the benefit of co-administration outweighs the risk. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended.

Co-administration of delamanid with a strong inhibitor of CYP3A (KALETRA) may slightly increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with KALETRA is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4,5).

***Antipsychotics***

Due to CYP3A inhibition by KALETRA, concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities (see section 4,5).

***Corticosteroids***

Concomitant use of KALETRA 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 adrenocortical suppression.

Concomitant use of KALETRA 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 KALETRA has been co-administered with inhaled or intranasally administered fluticasone propionate, budesonide, or injectable triamcinolone (see section 4,5).

***PDE5 inhibitors***

Co-administration of (KALETRA) with avanafil is not recommended.

Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving 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, and prolonged erection.

*Sildenafil*

Concomitant use of sildenafil with lopinavir/ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients (see section 4,3 and 4,5).

*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***

Patients on KALETRA should not use products containing St. John's Wort *(Hypericum perforatum)* because co-administration may be expected to reduce plasma concentrations of protease inhibitors. This may result in loss of therapeutic effect and development of resistance to lopinavir or to the therapeutic class of protease inhibitors (see section 4,3 and 4,5).

***HMG-CoA Reductase Inhibitors***

Concomitant use of KALETRA with lovastatin or simvastatin is contraindicated (see section 4,3). Caution should be exercised if HIV protease inhibitors, including lopinavir/ritonavir, are used concurrently with rosuvastatin or with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (e.g.atorvastatin), as this may increase the potential for serious reactions such as myopathy, including rhabdomyolysis (see section 4,3).

***Toxicity in Preterm Neonates***

A safe and effective dose of KALETRA SOLUTION in the preterm neonate population has not been established. KALETRA SOLUTION contains the excipients alcohol (42,4 % v/v) and propylene glycol (15,3 % w/v). KALETRA SOLUTION should not be used in preterm neonates in the immediate postnatal period because of possible toxicities (see section 4,4 "Paediatric Use" and 4,9).

When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at an increased risk of propylene glycol-associated adverse events due to diminished ability to metabolise propylene glycol, thereby leading to accumulation and potential adverse events. Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients. Infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to KALETRA SOLUTION including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma and apnoea), seizures, hypotonia, cardiac dysrhythmias and ECG changes, and haemolysis. Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving KALETRA SOLUTION.

***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, such as KALETRA. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic medicines 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. Consideration should be given to the monitoring of blood glucose.

***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.

***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 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 KALETRA 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 KALETRA in conjunction with other antiretroviral medicines. In some cases, the hepatic dysfunction was serious; however, a definitive 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, such as KALETRA. 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.

***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.

***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 section 4,5 for additional information on potential medicine 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.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

***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.

***Use in the elderly***

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.

For paediatric use of KALETRA SOLUTION, see section 4,2; 4,4 and 4,9.

In HIV-infected patients aged six months to 18 years, the adverse event profile seen during clinical trial was similar to that for adult patients. KALETRA should not be administered once daily in paediatric patients.

KALETRA SOLUTION contains high concentration of alcohol (42,4 % v/v) and 15,3 % propylene glycol (w/v).

Patients taking the oral solution, particularly those with renal impairment or with decreased ability to metabolise propylene glycol (e.g. those of Asian origin), should be monitored for adverse reactions potentially related to propylene glycol toxicity (i.e. seizures, stupor, tachycardia, hyperosmolarity, lactic acidosis, renal toxicity, haemolysis) (see section 4,3).

Besides propylene glycol as described above, KALETRA SOLUTION contains alcohol (42,4 % v/v) which is potentially harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children. It may modify or increase the effects of other medicines.
KALETRA SOLUTION contains sugar (up to 0,8 g of fructose per dose when taken according to the dosage recommendations). This may be unsuitable in hereditary fructose intolerance.

KALETRA SOLUTION contains up to 0,3 g of glycerol per dose. Only at high inadvertent doses, it can cause headache and gastrointestinal upset.

Furthermore, polyoxol 40 hydrogenated castor oil and potassium present in KALETRA SOLUTION may cause only at high inadvertent doses gastrointestinal upset. Patients on a low potassium diet should be cautioned.

Particular risk of toxicity in relation to the amount of alcohol and propylene glycol contained in KALETRA SOLUTION

Healthcare professionals should be aware that KALETRA SOLUTION is highly concentrated and contains 42,4 % alcohol (v/v) and 15,3 % propylene glycol (w/v). Each 1 ml of KALETRA SOLUTION contains 356,3 mg of alcohol and 152,7 mg of propylene glycol.

Special attention should be given to accurate calculation of the dose of KALETRA SOLUTION, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors and overdose. This is especially important for infants and young children.

Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients. Infants should be monitored closely for toxicity related to KALETRA SOLUTION including: hyperosmolality, with or without lactic acidosis, renal toxicity, central nervous system (CNS) depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac dysrhythmias and ECG changes, and hemolysis. Postmarketing life-threatening cases of cardiac toxicity (including complete atrioventricular (AV) block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving KALETRA SOLUTION (see sections 4,3 and 4,9).

Based on the findings in a paediatric study (observed exposures were approximately 35 % AUC12 and 75 % lower Cmin than in adults), young children from 14 days to 3 months could have sub-optimal exposure with a potential risk of inadequate virologic suppression and emergence of resistance (see section 5,2).

Because KALETRA SOLUTION contains alcohol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility.

### 4.5 Interaction with other medicinal products and other forms of interaction

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. Medicines 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 4 under section 4,3.

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.

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

***ANTI-HIV MEDICINES***

***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 anti-HIV medicines*

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.

*Rilpivirine*

Concomitant use of KALETRA 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 KALETRA 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)***

*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 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 with 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.

***Hepatitis C direct acting antivirals***

*Boceprevir*

Concomitant administration of boceprevir and KALETRA resulted in reduced boceprevir and lopinavir steady state exposure. It is not recommended to co-administer KALETRA and boceprevir.

*Glecaprevir/pibrentasvir:*

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

*Ombitasvir/paritaprevir/ritonavir and dasabuvir:*

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

*Simeprevir*

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

*Sofosbuvir/velpatasvir/voxilaprevir:*

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

*Telaprevir*

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

***HIV CCR5 – antagonist***

*Maraviroc*

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

***OTHER MEDICINES***

***Analgesic***

*Fentanyl:*KALETRA 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 KALETRA.

***Antidysrhythmics*** [*amiodarone, bepridil, dronedarone (see section 4,3) 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 KALETRA with digoxin, with appropriate monitoring of serum digoxin levels.

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

May have their serum concentrations increased when co-administered with KALETRA resulting in the potential for increased adverse events, some of which may be serious. Coadministration of venetoclax or ibrutinib with KALETRA could increase venetoclax or ibrutinib exposure potentially

resulting in a serious risk of tumor lysis syndrome. Coadministration of encorafenib or ivosidenib with KALETRA 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 professional information for dosing instructions.

Coadministration of apalutamide is contraindicated with KALETRA since apalutamide may decrease exposure of KALETRA with potential loss of virologic response. In addition, co-administration of apalutamide and KALETRA may lead to increased exposure of apalutamide resulting in increased potential for adverse events including seizure.

***Anticoagulants***

*Dabigatran etexilate and Edoxaban:Serum concentrations may be increased due to P-gp inhibition by KALETRA.* Clinical monitoring and/or dose reduction of the direct oral anticoagulants (DOAC) should be considered when a DOAC transported by P-gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co-administered with Kaletra.

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

*Rivaroxaban*: Co-administration of rivaroxaban and KALETRA may increase rivaroxaban exposure which may increase the risk of bleeding.

***Anticonvulsants***

*Phenobarbital (phenobarbitone), phenytoin, carbamazepine*:

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

*Lamotrigine and valproate:*

Co-administration of KALETRA and either of these medicines was associated with a reduction in the 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 KALETRA and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments.

***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 KALETRA, the combination should be used with caution and a lower dose of trazodone should be considered.

**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 KALETRA and voriconazole is not recommended.

***Antigout Medicines***

Concentrations of colchicine are expected to increase when co-administered with KALETRA. Life-threatening and fatal medicine interactions have been reported in patients treated with colchicine and ritonavir (see section 4,3 & 4,4). Refer to the colchicine professional information for prescribing information.

***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.

**Anti-mycobacterial**

*Rifabutin*

When rifabutin and KALETRA were co-administered for 10 days, rifabutin (parent drug and active 25-O-desacetyl metabolite) Cmax 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 medicines. 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.

*Bedaquiline:* In a healthy volunteer medicine interaction study of 400 mg single dose bedaquiline and KALETRA 400/100 mg twice daily for 24 days, bedaquiline exposures (AUC) were increased by 22 %. Bedaquiline must be used cautiously with KALETRA, only if the benefit of co-administration outweighs the risk. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4,4).

*Delamanid:* In a healthy volunteer medicine interaction study of delamanid 100 mg twice daily and KALETRA 400/100 mg twice daily for 14 days, exposures of delamanid and a delamanid metabolite, DM-6705, were slightly increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with KALETRA is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4,4).

***Antiparasitic***

*Atovaquone*

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

**Antipsychotics**

Concomitant use of quetiapine with KALETRA is contraindicated. Due to CYP3A inhibition by KALETRA, concentrations of quetiapine are expected to increase thus leading to quetiapine-related toxicities (see section 4.3).

***Corticosteroid***

*Dexamethasone*

Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations.

*Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone:*

Concomitant use of KALETRA 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 adrenocortical suppression. Consider alternatives to fluticasone propionate, budesonide, and injectable triamcinolone, particularly for long-term use (see section 4,4).

***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 dependent 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.

*Lomitapide*

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

***Immunosuppressants***

Concentrations of these medicines (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.

***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.

***Vasodilating medicines***

Co-administration of bosentan and KALETRA increased steady-state bosentan maximum concentrations ($C_{max}$) and area under the curve (AUC) by 6-fold and 5-fold, respectively. Please refer to the bosentan Professional information for prescribing information.

***PDE5 Inhibitors***

*Avanafil*

Co-administration of KALETRA with avanafil is expected to result in large increases in avanafil exposure and is not recommended (see section 4,4).

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

***Kinase Inhibitors (also see anticancer agents above)***

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

***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 section 4,3)

*Clinically Significant Medicine Interactions Not Expected*

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

Clinical studies showed no clinically significant interaction between KALETRA and raltegravir.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

The safety of KALETRA in pregnant women has not been established, as there are no adequate and well-controlled studies in pregnant women.

***Human Data***

*Risk Summary*

KALETRA has been evaluated in 3,366 women during pregnancy. Available human data suggest that lopinavir/ritonavir does not increase the risk of overall major birth defects compared to the background rate.

*Antiretroviral Pregnancy Registry*

In post-marketing surveillance through the Antiretroviral Pregnancy Registry (APR), established since January 1989, no increased risk of birth defects has been reported among over 1000 women exposed to KALETRA in the first trimester.

**Breastfeeding**

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.

### 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 and dizziness has been reported during treatment with KALETRA (see section 4,8).

Kaletra oral solution contains approximately 42 % v/v alcohol.

### 4.8 Undesirable effects

**a. Summary of the safety profile**

Not applicable

**b. Tabulated summary of adverse reactions**

*Adults*

Treatment-Emergent Adverse Events

The safety of KALETRA has been investigated in over 2,600 patients in Phase II-IV clinical trials, of which more than 700 have received a dose of 800/200 mg (4 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies, KALETRA was used in combination with efavirenz or nevirapine.

Commonly reported adverse reactions to KALETRA included diarrhoea, nausea, vomiting, hypertriglyceridaemia and hypercholesterolaemia. Diarrhoea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridaemia and hypercholesterolaemia may occur later.

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** | | |
|---|---|---|
| Infections and infestations | Very common | Upper respiratory tract infection |
| | Common | Lower respiratory tract infection, skin infections including cellulitis, folliculitis and furuncle |
| Blood and lymphatic system disorders | Common | Anaemia, leucopenia, lymphadenopathy and neutropenia |
| Immune system disorders | Common | Hypersensitivity including urticaria and angioedema |
| | Uncommon | Immune reconstitution inflammatory syndrome |
| Endocrine disorders | Uncommon | Hypogonadism |

| Undesirable Effects in Clinical Studies in Adult Patients | | |
|---|---|---|
| Metabolic and nutritional disorders | Common | Blood glucose disorders including diabetes mellitus, hyperglycaemia, decreased appetite, hypercholesterolemia, hypertriglyceridaemia, lactic acidosis, weight decreased |
| | Uncommon | increased appetite, weight gain |
| Psychiatric disorders | Common | Anxiety |
| | Uncommon | Abnormal dreams, decreased libido |
| Nervous System disorders | Common | Headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, insomnia |
| | Uncommon | tremor, convulsion |
| Eye disorders | Uncommon | Vision impairment |
| Ear and labyrinth disorders | Uncommon | Tinnitus, vertigo |
| Cardiac disorders | Uncommon | Atherosclerosis such as myocardial infarction, angina pectoris, atrioventricular block, tricuspid valve incompetence |
| Vascular disorders | Common | Hypertension |
| | Uncommon | Vasodilation, deep thrombophlebitis |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Dyspnoea, rhinitis, asthma, lung oedema, cough increased |
| Gastrointestinal disorders | Very common | Diarrhoea, nausea |
| | Common | Vomiting, abdominal pain (upper and lower), abnormal stools, dyspepsia, flatulence, |

| Undesirable Effects in Clinical Studies in Adult Patients | | |
|---|---|---|
| | | gastroesophageal reflex disease, gastroenteritis, pancreatitis, colitis, abdominal distension, haemorrhoids, |
| | Uncommon | Gastrointestinal haemorrhage including gastrointestinal ulcer, duodenitis, gastric ulcer constipation, dry mouth, faecal incontinence, gastritis, rectal haemorrhage, mouth ulcerations, stomatitis, |
| Hepatobiliary disorders | Common | Hepatitis including increase in AST, ALT and GGT |
| | Uncommon | Cholangitis, hepatomegaly, hyperbilirubinaemia, hepatic steatosis |
| | Very Rare | Jaundice |
| Skin and subcutaneous disorders | Common | Rash, including maculopapular rash,dermatitis/rash including eczema, seborrheic dermatitis, night sweat, pruritus |
| | Uncommon | Alopecia, capillaritis, vasculitis, dry skin, exfoliative dermatitis |
| | Very rare | Stevens-Johnson syndrome, erythema multiforme |
| Musculoskeletal and connective tissue disorders | Common | Myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such as weakness and spasms |
| | Uncommon | Osteonecrosis, rhabdomyolysis |
| Renal and urinary disorders | Uncommon | Nephritis, decreased creatinine clearance, haematuria |

| Undesirable Effects in Clinical Studies in Adult Patients | | |
|---|---|---|
| Reproductive system and breast disorders | Common | Erectile dysfunction, menstrual disorders-amenorrhoea, menorrhagia |
| | Uncommon | Ejaculation disorder, breast enlargement, gynaecomastia |
| General disorders and administration site conditions | Commonr | Fatigue including asthenia |

**c. Description of selected adverse reactions**

*Postmarketing Experience*

*Hepatobiliary disorders:* Hepatitis has been reported in patients on **KALETRA** therapy.

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

*Cardiac disorders:* Bradysrhythmia has been reported.

*Renal and urinary disorders:* Nephrolithiasis.

**d. Paediatric population**

*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/m2) 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/litre | 2 % | 2 % | 3 % | 1 % | 4 % |
| Uric Acid | > 0,71 mmol/litre | 2 % | 2 % | 0 % | 3 % | 3 % |
| SGOT/AST | > 180 U/litre | 2 % | 4 % | 5 % | 3 % | 9 % |
| SGPT/ALT | > 215 U/litre | 4 % | 4 % | 4 % | 3 % | 9 % |
| GGT | > 300 U/litre | N/A | N/A | N/A | N/A | 6 % |
| Total cholesterol | > 7,77 mmol/litre | 9 % | 5 % | 3 % | 3 % | 22 % |
| Triglycerides | > 8,25 mmol/litre | 9 % | 1 % | 5 % | 4 % | 22 % |
| Amylase | > 2[1] ULN | 3 % | 2 % | 7 % | 5 % | 4 % |
| **Haematology** | **Low** | | | | | |
| Neutrophils | 0,75 x $10^9$/litre | 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/ litre | 1 % | 2 % | 5 % |
| Total bilirubin | > 59,5 mcmol/ litre | 1 % | 3 % | 1 % |
| SGOT/AST | > 180 U/ litre | 5 % | 11 % | 8 % |
| SGPT/ALT | > 215 U/ litre | 6 % | 13 % | 10 % |
| GGT | > 300 U/ litre | N/A | N/A | 29 % |
| Total cholesterol | > 7,77 mmol/ litre | 20 % | 21 % | 39 % |
| Triglycerides | > 8,25 mmol/ litre | 25 % | 21 % | 36 % |
| Amylase | > 2[1] ULN | 4 % | 8 % | 8 % |
| **Chemistry** | **Low** | | | |
| Inorganic Phosphorous | < 0,48 mmol/ litre | 1 % | 0 % | 2 % |
| **Haematology** | **Low** | | | |
| Neutrophils | 0,75 x $10^9$/ litre | 1 % | 2 % | 4 % |

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

| | | 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) |

[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/ litre | 7,0 % |
| SGPT/ALT | > 215 x U/ litre | 4,0 % |
| Total cholesterol | > 7,77 mmol/ litre | 2,0 % |
| Amylase | > 2,5 x ULN | 4,0 % |
| **Chemistry** | **Low** | |
| Sodium | < 130 mmol/ litre | 3,0 % |
| **Haematology** | **Low** | |
| Platelet Count | < 50 x $10^9$/ litre | 4,0 % |
| Neutrophils | <0,40 x $10^9$/ litre | 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.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publication: https://www.sahpra.org.za/Publications/Index/8

Healthcare professionals, patients and caregivers are also asked to report any suspected adverse reaction to AbbVie (Pty) Ltd via this e-mail address: MEAPV@abbvie.com

### 4.9 Overdose

Side effects can be exacerbated and exaggerated with overdose. The following events have been reported in association with unintended overdoses in pre-term neonates: complete AV block, cardiomyopathy, lactic acidosis, and acute renal failure. KALETRA SOLUTION contains 42,4 % alcohol (v/v) and 15,3 % propylene glycol (w/v) which would result into significant alcohol toxicity in young children after overdose (see section 2; 4,2 and 4,4).

Treatment of overdose with KALETRA should consists of symptomatic and 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. 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. However, dialysis can remove both alcohol and propylene glycol in the case of overdose with KALETRA SOLUTION.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Class of Medicines: A 20.2.8 - Antiviral Medicines**

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.

**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. 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*

Administration of a single 400/100 mg dose of lopinavir/ritonavir oral solution with a moderate fat meal (500 – 682 kcal, 22,7 to 25,1 % calories from fat) was associated with a mean increase of 80 and 54 % in lopinavir AUC and $C_{max}$, 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 and 130 and 56 %, respectively for oral solution, relative to fasting. To enhance bioavailability and minimise pharmacokinetic variability lopinavir/ritonavir should be taken with food.

After multiple dosing with 400/100 mg lopinavir/ritonavir b.i.d. with food for three weeks lopinavir peak plasma concentration ($C_{max}$) of 12,3 ±.4 micrograms/mℓ, occurred at four hours ($T_{max}$).

*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.

*Biotransformation*

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 14days.

*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 litre/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 two weeks without meal restriction (n = 16) produced a mean ± SD lopinavir $C_{max}$ of 14,8 ± 3,5 µg/ml, occurring approximately six hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 5,5 ± 5,4 µg/ml and minimum concentration within a dosing interval was 3,2 ± 3,4 µg/ml. Lopinavir AUC over a 24 hour dosing interval averaged 206,5 ± 8,7 µg.h/ml.

***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).

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 section 4.4).

## 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

**KALETRA SOLUTION:**

alcohol 42.4 % v/v,

high fructose corn syrup,

propylene glycol 15,3 % w/v

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.

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

24 months

## 6.4 Special precautions for storage

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.

**6.5 Nature and contents of container <and special equipment for use, administration or implantation**

**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.

**6.6 Special precautions for disposal of the used medicine or waste derived from such medicine and other handling of product**

Not applicable

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

ABBVIE (PTY) LTD

Building 7, Waterfall Corporate Campus

74 Waterfall Drive

Waterfall City

Midrand, 1685

South Africa

## 8. REGISTRATION NUMBER (S)

**KALETRA SOLUTION :** 35/20.2.8/0255

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

05 AUGUST 2002

## 10. DATE OF REVISION OF THE TEXT

25 JUNE 2024

CCDS03080220