Kaluvia®

Lopinavir / Ritonavir

FORMS AND PRESENTATION

Kaluvia®: Film coated tablets: Jar of 60.

COMPOSITION

Kaluvia®: Each film coated tablet contains Lopinavir 200mg and Ritonavir 50mg.

Excipients: copovidone, colloidal silicon dioxide, sorbitan monolaurate, sodium stearyl fumarate, silica, yellow iron oxide, hydroxypropyl methylcellulose, talc, titanium dioxide, polyethylene glycol, polysorbate, hydroxypropyl cellulose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Antivirals for systemic use.

ATC code: J05AE06.

Lopinavir provides the antiviral activity of Kaluvia®. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus.

Pharmacokinetic properties

Absorption

Multiple dosing with 400/100 mg Kaluvia® twice daily for 2 weeks and without meal restriction produced a mean ± SD Lopinavir peak plasma concentration (C_{max}) of 12.3 ± 5.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 113.2 ± 60.5 µg•h/ml. The absolute bioavailability of Lopinavir co-formulated with Ritonavir in humans has not been established.

Administration of a single 400/100 mg dose of Kaluvia® tablets under fed conditions (high fat, 872 kcal, 56% from fat) compared to fasted state was associated with no significant changes in C_{max} and AUC_{inf}. Therefore, Kaluvia® tablets may be taken with or without food.

Distribution

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

Biotransformation

In vitro experiments with human hepatic microsomes indicate that Lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of Lopinavir and therefore, increases plasma levels of Lopinavir.

Elimination

After 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 feces, respectively. Unchanged Lopinavir accounted for approximately 2.2% and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the Lopinavir dose is excreted unchanged in the urine. The effective (peak to trough) half-life of Lopinavir over a 12 hour dosing interval averaged 5 − 6 hours, and the apparent oral clearance (CL/F) of Lopinavir is 6 to 7 l/h.

As compared to the twice daily regimen, the once daily dosing is associated with a reduction in the C_{min}/C_{trough} values of approximately 50%.

INDICATIONS

Kaluvia® is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults, adolescents and children above the age of 2 years.

The choice of Kaluvia® to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Patients with severe hepatic insufficiency.
- Kaluvia® contains Lopinavir and Ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Kaluvia® should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. These medicinal products include astemizole, terfenadine, oral midazolam, triazolam, cisapride, pimozide, amiodarone, ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine), lovastatin, simvastatin, sildenafil used for the treatment of pulmonary arterial hypertension and vardenafil.
- Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking Lopinavir and Ritonavir due to the risk of decreased plasma concentrations and reduced clinical effects of Lopinavir and Ritonavir.

PRECAUTIONS

- Hepatic impairment: The safety and efficacy of Kaluvia® has not been established in patients with significant underlying liver disorders. Kaluvia® is contraindicated in patients with severe liver impairment. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and in individuals treated for post-exposure prophylaxis as early as 7 days after the initiation of Kaluvia® in conjunction with other antiretroviral agents. In some cases the hepatic dysfunction was serious.

Appropriate laboratory testing should be conducted prior to initiating therapy with Kaluvia® and close monitoring should be performed during treatment.

- Renal impairment: Since the renal clearance of Lopinavir and Ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because Lopinavir and Ritonavir are highly protein bound, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.
- Hemophilia: There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship had been evoked, although the mechanism of action had not been elucidated. Hemophiliac patients should therefore be made aware of the possibility of increased bleeding.
- Lipid elevations: Treatment with Kaluvia® has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing is to be performed prior to initiating Kaluvia® therapy and at periodic intervals during therapy. Particular caution should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders are to be managed as clinically appropriate.
- Pancreatitis: Cases of pancreatitis have been reported in patients receiving Kaluvia®, including those who developed hypertriglyceridemia. In most of these cases patients have had a prior history of pancreatitis and/or concurrent therapy with other medicinal products associated with pancreatitis. Marked triglyceride elevation is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and Kaluvia® therapy should be suspended if a diagnosis of pancreatitis is made.

- Hyperglycemia: New onset diabetes mellitus, hyperglycemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these the hyperglycemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycemia.
- Fat redistribution and metabolic disorders: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesized. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.
- Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.
- 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.
- PR interval prolongation: Kaluvia® has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atroventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving Kaluvia®. Kaluvia® should be used with caution in such patients.
- Interactions with medicinal products: Kaluvia® contains Lopinavir and Ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Kaluvia® is likely to increase plasma concentrations of medicinal products that are primarily metabolized by CYP3A. These increases of plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events.

The combination of Kaluvia® with atorvastatin is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring. Caution must also be exercised and reduced doses should be considered if Kaluvia® is used concurrently with rosuvastatin.

If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Particular caution should be used when prescribing PDE5 inhibitors such as sildenafil or tadalafil for the treatment of erectile dysfunction in patients receiving Kaluvia®. Co-administration of Kaluvia® with these medicinal products is expected to substantially increase their concentrations and may result in associated adverse events such as hypotension, syncope, visual changes and prolonged erection. Concomitant use of vardenafil and Kaluvia® is contraindicated. Concomitant use of sildenafil prescribed for the treatment of pulmonary arterial hypertension with Kaluvia® is contraindicated.

Particular caution must be used when prescribing Kaluvia® and medicinal products known to induce QT interval prolongation such as: chlorpheniramine, quinidine, erythromycin, and clarithromycin. Indeed, Kaluvia® could increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac adverse reactions. Cardiac events have been reported with Kaluvia® in preclinical studies; therefore, the potential cardiac effects of Kaluvia® cannot be currently ruled out.

Co-administration of Kaluvia® with rifampicin is not recommended. Rifampicin in combination with Kaluvia® causes large decreases in Lopinavir concentrations which may in turn significantly decrease the Lopinavir therapeutic effect. Adequate exposure to Kaluvia® may be achieved when a higher dose of Kaluvia® is used but this is associated with a higher risk of liver and gastrointestinal toxicity. Therefore, this co-administration should be avoided unless judged strictly necessary.

Concomitant use of Kaluvia® and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

- Other: Kaluvia® is not a cure for HIV infection or AIDS. It does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Appropriate precautions should be taken. People taking Kaluvia® may still develop infections or other illnesses associated with HIV disease and AIDS.

Ability to drive and use machines

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

PREGNANCY AND LACTATION

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterize the safety for the fetus.

Studies in rats revealed that Lopinavir is excreted in the milk. It is not known whether this medicinal product is excreted in human milk. As a general rule, it is recommended that mothers infected by HIV do not breastfeed their babies under any circumstances in order to avoid transmission of HIV.

Animal studies have shown no effects on fertility. No human data on the effect of Kaluvia® on fertility are available.

DRUG INTERACTIONS

Unless otherwise stated, studies detailed below have been performed with the recommended dosage of Kaluvia® (i.e. 400/100 mg twice daily).

- Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs): Abacavir and zidovudine concentrations may be reduced due to increased glucuronidation by Kaluvia®. The clinical significance of reduced abacavir and zidovudine concentrations is unknown.

Co-administration of tenofovir 300 mg once daily and Kaluvia® increased tenofovir AUC by 32% and Cmin by 51%. No dose adjustment is necessary. Higher tenofovir concentrations could potentiate tenofovir associated adverse events, including renal disorders.

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs): Co-administration of efavirenz 600 mg once daily and Kaluvia® decreased Lopinavir AUC by 20%, C_{max} by 13% and C_{min} by 42%. No changes in Lopinavir AUC, C_{max} or C_{min} were detected when co-administering efavirenz 600 mg once daily and Kaluvia® 500/125 mg twice daily (Relative to 400/100 mg twice daily administered alone). The Kaluvia® tablets dosage should be increased to 500/125 mg twice daily when co-administered with efavirenz. Kaluvia® must not be administered once daily in combination with efavirenz.

Co-administration of nevirapine 200 mg twice daily and Kaluvia® decreased Lopinavir AUC by 27%, C_{max} by 19% and C_{min} by 51%. The Kaluvia® tablets dosage should be increased to 500/125 mg twice daily when co-administered with nevirapine. Kaluvia® must not be administered once daily in combination with nevirapine.

- Co-administration with other HIV protease inhibitors (PIs): According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.

Co-administration of increased doses of fosamprenavir (1400 mg twice daily) with Lopinavir/Ritonavir (533/133 mg twice daily) to protease inhibitor-experienced patients resulted in a higher incidence of gastrointestinal adverse events and elevations in triglycerides with the combination regimen without increases in virological efficacy, when compared with standard doses of fosamprenavir/Ritonavir. Concomitant administration of these medicinal products is not recommended. Kaluvia® must not be administered once daily in combination with amprenavir.

The co-administration of nelfinavir and Kaluvia® resulted in decreased concentrations of Lopinavir. The appropriate doses for this combination, with respect to efficacy and safety, have not been established. Kaluvia® must not be administered once daily in combination with nelfinavir.

Co-administration of tipranavir/Ritonavir 500/100 mg twice daily and Kaluvia® decreased Lopinavir AUC by 55%, C_{max} by 47% and C_{min} by 70%. Concomitant administration of these medicinal products is not recommended.

- Analgesics: Co-administration of fentanyl and Kaluvia® resulted in an increased risk of side-effects (respiratory depression, sedation) due to higher plasma concentrations because of CYP3A4 inhibition by Kaluvia®. Careful monitoring of adverse effects (notably respiratory depression but also sedation) is recommended when fentanyl is concomitantly administered with Kaluvia®.
- Antiarrhythmics: Co-administration of digoxin and Kaluvia® resulted in increased plasma concentrations of due to P-glycoprotein inhibition by Kaluvia®. The increased digoxin level may lessen over time as Pgp induction develops. Caution is warranted and therapeutic drug monitoring of digoxin concentrations, if available, is recommended in case of co-administration of Kaluvia® and digoxin. Particular caution should be used when prescribing Kaluvia® in patients taking digoxin as the acute inhibitory effect of Ritonavir on Pgp is expected to significantly increase digoxin levels. Initiation of digoxin in patients already taking Kaluvia® is likely to result in lower than expected increases of digoxin concentrations.

Bepridil, systemic lidocaine and quinidine concentrations may be increased when co-administered with Kaluvia®. Caution is warranted and therapeutic drug concentration monitoring is recommended when available.

- Antibiotics: Moderate increases in clarithromycin AUC are expected due to CYP3A inhibition by Kaluvia®. For patients with renal impairment (CrCL <30 ml/min) dose reduction of clarithromycin should be considered. Caution should be exercised in administering clarithromycin with Kaluvia® to patients with impaired hepatic or renal function.
- Anticancer agents: There is a risk of increased adverse events when co-administering most tyrosine kinase inhibitors such as dasatinib or nilotinib, also vincristine or vinblastine and Kaluvia® due to higher serum concentrations because of CYP3A4 inhibition by Kaluvia®. Careful monitoring of the tolerance of these anticancer agents is recommended.
- Anticoagulants: Concentrations may be affected when warfarin is co-administered with Kaluvia® due to CYP2C9 induction. It is recommended that INR (international normalized ratio) be monitored.
- Anticonvulsants: Steady-state concentrations of phenytoin were moderately decreased due to CYP2C9 and CYP2C19 induction by Kaluvia®. Also, Lopinavir concentrations are decreased due to CYP3A induction by phenytoin. Caution should be exercised in administering phenytoin with Kaluvia®. Phenytoin levels should be monitored when co-administering with Kaluvia®. When co-administered with phenytoin, an increase of Kaluvia® dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. Kaluvia® must not be administered once daily in combination with phenytoin.

Carbamazepine serum concentrations may be increased due to CYP3A inhibition by Kaluvia®.

Also, Lopinavir concentrations may be decreased due to CYP3A induction by carbamazepine and phenobarbital. Caution should be exercised and carbamazepine and phenobarbital levels should be monitored when co-administered with Kaluvia®. When co-administered with carbamazepine or phenobarbital, an increase of Kaluvia® dosage may be envisaged. Dose adjustment has not been evaluated in clinical practice. Kaluvia® must not be administered once daily in combination with carbamazepine and phenobarbital.

per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for Kaluvia®.

Large decreases in Lopinavir concentrations may be observed when co-administered with rifampicin due to CYP3A induction by rifampicin. Co-administration of Kaluvia® with rifampicin is not recommended as the decrease in Lopinavir concentrations may in turn significantly decrease the Lopinavir therapeutic effect A dose adjustment of Kaluvia® 400/400 mg (i.e. Kaluvia® 400/100 mg + Ritonavir 300 mg) twice daily has allowed compensating for the CYP 3A4 inducer effect of rifampicin. However, such a dose adjustment might be associated with ALT/AST elevations and with increase in gastrointestinal disorders. Therefore, this co-administration should be avoided unless judged strictly necessary. If this co-administration is judged unavoidable, increased dose of Kaluvia® at 400/400 mg twice daily may be administered with rifampicin under close safety and therapeutic drug monitoring. The Kaluvia® dose should be titrated upward only after rifampicin has been initiated.

- Benzodiazepines: Co-administration of midazolam and Kaluvia® resulted in an increase in oral midazolam AUC by 13-fold and an increase in parenteral midazolam AUC by 4-fold due to CYP3A inhibition by Kaluvia®. Kaluvia® must not be co-administered with oral midazolam, whereas caution should be used with co-administration of Kaluvia® and parenteral midazolam. If Kaluvia® is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered especially if more than a single dose of midazolam is administered.
- Calcium channel blockers: Felodipine, nifedipine and nicardipine concentrations may be increased due to CYP3A inhibition by Kaluvia®. Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with Kaluvia®.
- Corticosteroids: Lopinavir concentrations may be decreased due to CYP3A induction by dexamethasone. Clinical monitoring of antiviral efficacy is recommended when these medicines are concomitantly administered with Kaluvia®.

Fluticasone propionate plasma concentrations increase and cortisol levels decrease by 86% when co-administering fluticasone propionate 50 µg intranasal 4 times daily with Ritonavir 100 mg twice daily. Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving Ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolized via the P450 3A pathway e.g. budesonide. Consequently, concomitant administration of Kaluvia® and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period.

- Erectile Dysfunction, Phosphodiesterase (PDE5) inhibitors: when co-administered with Kaluvia®, tadalafil AUC is increased by 2-fold, sildenafil AUC is increased by 11-fold and vardenafil AUC is increased by 49-fold due to CYP3A inhibition by Kaluvia®. Particular caution must be used when prescribing sildenafil or tadalafil in patients receiving Kaluvia® with increased monitoring for adverse events including hypotension, syncope, visual changes and prolonged erection. When co-administered with Kaluvia®, sildenafil doses must not exceed 25 mg in 48 hours and tadalafil doses must not exceed 10 mg every 72 hours. Co-administration of Kaluvia® with sildenafil used for the treatment of pulmonary arterial hypertension is contra-indicated. The use of vardenafil with Kaluvia® is contraindicated.
- Herbal products: Lopinavir concentrations may be reduced due to induction of CYP3A by the herbal preparation St John's wort (Hypericum perforatum). Herbal preparations containing St John's wort must not be combined with Lopinavir and Ritonavir. If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Lopinavir and Ritonavir levels may increase on stopping St John's wort. The dose of Kaluvia® may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort. Therefore, Kaluvia® can be started safely 2 weeks after cessation of St. John's wort.
- Immunosuppressants: When co-administered with Kaluvia®, cyclosporin, sirolimus (rapamycin) and tacrolimus concentrations may be increased due to CYP3A inhibition by Kaluvia®. More frequent therapeutic concentration monitoring is recommended until plasma levels of these products have been stabilized.
- Lipid lowering agents: Co-administration of lovastatin or simvastatin with Kaluvia® resulted in markedly increased plasma concentrations of lovastatin or simvastatin due to CYP3A inhibition by Kaluvia®. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these agents with Kaluvia® is contraindicated.

Co-administration of atorvastatin and Kaluvia® resulted in an increase of atorvastatin AUC by 5.9-fold and C_{max} by 4.7-fold due to CYP3A inhibition by Kaluvia®. The combination of Kaluvia® with atorvastatin is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring.

Co-administration of rosuvastatin and Kaluvia® resulted in an increase of rosuvastatin AUC by 2-fold and C_{max} by 5-fold. While rosuvastatin is poorly metabolized by CYP3A4, an increase of its plasma concentrations was observed. The mechanism of this interaction may result from inhibition of transport proteins. Caution should be exercised and reduced doses should be considered when Kaluvia® is co-administered with rosuvastatin.

As pravastatin is not metabolized by CYP450 and fluvastatin is partially metabolized by CYP2C9, if treatment with an HMG-CoA reductase inhibitor is indicated, fluvastatin or pravastatin is recommended.

- Opioids: Methadone concentrations are decreased when co-administered with Kaluvia®. Monitoring of plasma concentrations of methadone is recommended.
- Oral Contraceptives: Ethinyl oestradiol concentrations are decreased when co-administered with Kaluvia®. In case of co-administration of Kaluvia® with contraceptives containing ethinyl oestradiol (whatever the contraceptive formulation e.g. oral or patch), additional methods of contraception must be used.
- Smoking cessation aids: Co-administration of bupropion with Kaluvia® resulted in a decrease in AUC and C_{max} of buproprion and its active metabolite, hydroxybupropion by approximately 50%. This effect may be due to induction of bupropion metabolism. If the co-administration of Kaluvia® with bupropion is judged unavoidable, this should be done under close clinical monitoring for bupropion efficacy, without exceeding the recommended dosage, despite the observed induction.
- Other medicinal products: Based on known metabolic profiles, clinically significant interactions are not expected between Kaluvia® and dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole.

ADVERSE EFFECTS

The most common adverse reactions related to Kaluvia® therapy during clinical trials were diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. The risk of diarrhea may be greater with once daily dosing of Kaluvia®. Diarrhea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridemia and hypercholesterolemia may occur later. Treatment emergent adverse events led to premature study discontinuation for 7% of subjects from Phase II-IV studies.

It is important to note that cases of pancreatitis have been reported in patients receiving Kaluvia®, including those who developed hypertriglyceridemia. Furthermore, rare increases in PR interval have been reported during Kaluvia® therapy.

The following events have been identified as adverse reactions. The frequency category includes all reported events of moderate to severe intensity, regardless of the individual causality assessment. The adverse reactions are displayed by system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and not known (cannot be estimated from the available data).

- Infections and infestations: Upper respiratory tract infection (very common); lower respiratory tract infection, skin infections including cellulitis, folliculitis and furuncle (common).
- Blood and lymphatic system disorders: Anemia, leucopenia, neutropenia, lymphadenopathy (common).
- Immune system disorders: Hypersensitivity including urticaria and angioedema (common); immune reconstitution syndrome (uncommon).
- Endocrine disorders: Hypogonadism (uncommon).
- Metabolism and nutrition disorders: Blood glucose disorders including diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, weight decreased, decreased appetite (common); weight increased, increased appetite (uncommon).
- Psychiatric disorders: Anxiety (common); abnormal dreams, libido decreased (uncommon).
- Nervous system disorders: Headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, insomnia (common); cerebrovascular accident, convulsion, dysgeusia, ageusia, tremor (uncommon).
- Eye disorders: Visual impairment (uncommon).
- Ear and labyrinth disorders: Tinnitus, vertigo (uncommon).
- Cardiac disorders: Atherosclerosis such as myocardial infarction, atrioventricular block, tricuspid valve incompetence (uncommon).
- Vascular disorders: Hypertension (common); deep vein thrombosis (uncommon).
- Gastrointestinal disorders: Diarrhea, nausea (very common); pancreatitis, vomiting, gastroesophageal reflux disease, gastroenteritis and colitis, abdominal pain (upper and lower), abdominal distension, dyspepsia, hemorrhoids, flatulence (common); gastrointestinal hemorrhage including gastrointestinal ulcer, duodenitis, gastritis and rectal hemorrhage, stomatitis and oral ulcers, fecal incontinence, constipation, dry mouth (uncommon).
- Hepatobiliary disorders: Hepatitis including AST, ALT and GGT increases (common); hepatic steatosis, hepatomegaly, cholangitis, hyperbilirubinemia (uncommon); jaundice (not known).
- Skin and subcutaneous tissue disorders: Lipodystrophy acquired including facial wasting, rash including maculopapular rash, dermatitis/rash including eczema and seborrheic dermatitis, night sweats, pruritis (common); alopecia, capillaritis, vasculitis (uncommon); Stevens-Johnson syndrome, erythema multiforme (not known).
- Musculoskeletal and connective tissue disorders: Myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such as weakness and spasms (common); rhabdomyolysis, osteonecrosis (uncommon).
- Renal and urinary disorders: Creatinine clearance decreased, nephritis, hematuria (uncommon).
- Reproductive system and breast disorders: Erectile dysfunction, menstrual disorders - amenorrhea, menorrhagia (common).
- General disorders and administration site conditions: Fatigue including asthenia (common).

Cushing's syndrome has been reported in patients receiving Ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolized via the P450 3A pathway e.g. budesonide.

Increased creatine phosphokinase (CPK), myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.

In children 2 years of age and older, the nature of the safety profile is similar to that seen in adults.

DOSAGE AND ADMINISTRATION

Kaluvia® should be prescribed by physicians who are experienced in the treatment of HIV infection.

Adult and adolescent use

The standard recommended dosage of Kaluvia® tablets is 400/100 mg (two 200/50 mg) tablets twice daily taken with or without food. In adult patients, in cases where once daily dosing is considered necessary for the management of the patient, Kaluvia® tablets may be administered as 800/200 mg (four 200/50 mg tablets) once daily with or without food. The use of a once daily dosing should be limited to those adult patients having only very few protease inhibitor (PI) associated mutations (i.e. less than 3 PI mutations in line with clinical trial results) and should take into account the risk of a lesser sustainability of the virologic suppression and higher risk of diarrhea compared to the recommended standard twice daily dosing.

Pediatric use (2 years of age and above)

The adult dose of Kaluvia® tablets (400/100 mg twice daily) may be used in children 40 kg or greater or with a Body Surface Area (BSA)* greater than 1.4 m^2.

* Body surface area can be calculated with the following equation:

BSA (m2) = √ (Height (cm) X Weight (kg) / 3600)

Children less than 2 years of age

The safety and efficacy of Kaluvia® in children aged less than 2 years have not yet been established. No recommendation on a posology can be made.

Concomitant Therapy: Efavirenz or nevirapine

The following table contains dosing guidelines for Kaluvia® tablets based on BSA when used in combination with efavirenz or nevirapine in children.

Pediatric dosing guidelines with concomitant efavirenz or nevirapine	
Body Surface Area (m^2)	Recommended Kaluvia® dosing (mg) twice daily.
≥ 0.5 to < 0.8	200/50 mg
≥ 0.8 to < 1.2	300/75 mg
≥ 1.2 to < 1.4	400/100 mg
≥ 1.4	500/125 mg

Hepatic impairment

In HIV-infected patients with mild to moderate hepatic impairment, an increase of approximately 30% in Lopinavir exposure has been observed but is not expected to be of clinical relevance. No data are available in patients with severe hepatic impairment. Kaluvia® must not be given to these patients.

Renal impairment

Since the renal clearance of Lopinavir and Ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because Lopinavir and Ritonavir are highly protein bound, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.

Method of administration

Kaluvia® tablets are administered orally and they can be taken with or without food.

OVERDOSAGE

To date, there is limited human experience of acute overdose with Kaluvia®.

The adverse clinical signs observed in dogs included salivation, emesis and diarrhea/abnormal stool. The signs of toxicity observed in mice, rats or dogs included decreased activity, ataxia, emaciation, dehydration and tremors.

There is no specific antidote for overdose with Kaluvia®. Treatment of overdose with Kaluvia® is to consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since Kaluvia® is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: January 2015.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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Manufactured by Hetero Labs Limited, India

Packed by **Benta** S.A.L., Lebanon