SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

ALUVIA 100/25 film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **ALUVIA 100/25** film-coated tablet contains 100 mg of lopinavir and 25 mg of ritonavir.

"Sugar free"

"for full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Pale pink film-coated tablets debossed with the code **"AC"** on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ALUVIA 100/25 film-coated tablet is indicated in combination with other antiretroviral medicines for the treatment of HIV-infection.

4.2 Posology and method of administration

ALUVIA 100/25 tablets may be taken with or without food. **ALUVIA 100/25** tablets should be swallowed whole and not chewed, broken or crushed.

ALUVIA 100/25 should be initiated by medical practitioners who are experienced in the treatment of HIV infection.

Posology

The recommended oral dose of **ALUVIA 100/25** film-coated tablets are as follows:

Adults

- **ALUVIA 100/25** film-coated tablets 400/100 mg (given as two, 200/50 mg tablets) twice daily with or without food.
- **ALUVIA 100/25 film**-coated tablets 800/200 mg (given as four, 200/50 mg tablets) once daily with or without food – in patients with less than three lopinavir-associated mutations. There are insufficient data to support the use of once daily administration of **ALUVIA 100/25 in** adult patients with three or more lopinavir-associated mutations.

ALUVIA 100/25 should not be administered once daily in combination with carbamazepine, phenobarbital or phenytoin.

Paediatric Patients

ALUVIA 100/25 should not be administered once daily in paediatric patients. The adult dose of **ALUVIA 100/25** film-coated tablets (two 200/50 mg tablets twice daily) may be used in children with a Body Surface Area (BSA)* greater than 1,3 m^2. **ALUVIA 100/25** film-coated tablets once daily have not been evaluated in paediatric patients.

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

$$\text{BSA } (m^2) = \sqrt{\frac{\text{Ht (Cm)} \times \text{Wt (kg)}}{3600}}$$

Paediatric Dosing Guidelines Based on BSA **(without concomitant efavirenz, nevirapine, nelfinavir or amprenavir)**	
Body Surface Area (m^2)	**Recommended number of ALUVIA 100/25 Tablets**
≥ 0,6 to < 0,9	2 tablets (200/50 mg) twice daily with or without food
≥ 0,9 to < 1,4	3 tablets (300/75 mg) twice daily with or without food
≥ 1,4	4 tablets (400/100 mg) twice daily with or without food

The following table contains dosing guidelines for **ALUVIA 100/25** tablets based on body weight.

Paediatric Dosing Guidelines Based on Body Weight (without concomitant efavirenz, nevirapine Nelfinavir or Amprenavir)		
Weight (kg)	**Dose (mg/kg)***	**Number of ALUVIA 100/25 tablets**
7 kg to < 15 kg	12 mg/kg twice daily	Tablets are not recommended. This formulation is not suitable for children weighing less than 15 kg use oral solution.
15 kg to 40 kg	10 mg/kg twice daily	
15 kg to 25 kg		2 tablets (200/50 mg) twice daily with or without food
> 25 kg to 35 kg		3 tablets (300/75 mg) twice daily with or without food
> 35 kg to 40 kg		4 tablets (400/100 mg) twice daily with or without food
> 40 kg	400 mg twice daily	4 tablets (400/100 mg) twice daily with or without food

* dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg lopinavir / 20 mg ritonavir per mL)

PLEASE NOTE:

-Use adult dosage recommendation for children > 12 years of age.

-Lopinavir/ritonavir oral solution is available to patients who cannot take a tablet formulation. Please refer to the professional information of the lopinavir/ritonavir oral solution for dosing instructions.

Concomitant Therapy

Omeprazole and Ranitidine

ALUVIA 100/25 film-coated tablets 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 **ALUVIA 100/25** to 500/125 mg twice daily (such as two 200/50 mg and one 100/25 mg tablet should be considered when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **section 4.5**).

ALUVIA 100/25 film-coated tablets should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

The following table contains dosing guidelines for **ALUVIA 100/25** film-coated tablets based on BSA when used in combination with efavirenz, nevirapine, nelfinavir or amprenavir in children:

Paediatric Dosing Guidelines Based on BSA **(with concomitant efavirenz, nevirapine, nelfinavir or amprenavir)**

Body Surface Area (m^2)	**Recommended number of ALUVIA 100/25 Tablets**
0,6 to < 0,8	2 tablets (200/50 mg) twice daily with or without food
≥ 0,8 to < 1,2	3 tablets (300/75 mg) twice daily with or without food
≥ 1,2	4 tablets (400/100 mg) twice daily with or without food

The following table contains dosing guidelines for **ALUVIA 100/25** film-coated tablets based on body weight when used in combination with efavirenz, nevirapine, nelfinavir or amprenavir in children:

Paediatric Dosing Guidelines Based on Body Weight (with concomitant efavirenz, nevirapine, nelfinavir or amprenavir)		
Weight (kg)	**Dose (mg/kg)***	**Number of ALUVIA 100/25 tablets**
7 kg to < 15 kg	13 mg/kg twice daily	Tablets are not recommended. This formulation is not suitable for children weighing less than 15 kg
15 kg to 45 kg	11 mg/kg twice daily	
15 kg to 20 kg		2 tablets (200/50 mg) twice daily with or without food

Paediatric Dosing Guidelines Based on Body Weight **(with concomitant efavirenz, nevirapine, nelfinavir or amprenavir)**		
Weight (kg)	**Dose (mg/kg)***	**Number of ALUVIA 100/25 tablets**
> 20 kg to 30 kg		3 tablets (300/75 mg) twice daily with or without food
> 30 kg to 45 kg		4 tablets (400/100 mg) twice daily with or without food
> 45 kg	400 mg or 600 mg twice daily	4 tablets (400/100 mg) twice daily with or without food 6 tablets (600/150 mg) twice daily with or without food

* dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg lopinavir / 20 mg ritonavir per mL)

Method of administration

ALUVIA 100/25 film-coated tablets are administered orally and must be swallowed whole and not chewed, broken or crushed. **ALUVIA 100/25** film-coated tablets can be taken with or without food.

4.3 Contraindications

ALUVIA 100/25 is contra-indicated in patients with known hypersensitivity to lopinavir, ritonavir or any of its excipients **(see section 6.1).**

ALUVIA 100/25 should not be co-administered concurrently with medicines that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These medicines are listed in **TABLE** 1.

TABLE 1: MEDICINES WHICH SHOULD NOT BE CO-ADMINISTERED WITH ALUVIA 100/25

Medicine Class	**Medicine within class not to be co-administered**
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL
Antianginal	Ranolazine
Antidysrhythmic	Dronedarone, amiodarone
Antibiotics	Fusidic acid
Anticancer medicines	Apalutamide Neratinib
Antigout	Colchicine in patients with renal and/or hepatic impairment
Antihistamines	Astemizole
Antipsychotics	Blonanserin, lurasidone ,pimozide , quetiapine
Benzodiazepines	Midazolam, triazolam

Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine
Prokinetic medicines	Cisapride
Herbal Products	St. John's Wort (*Hypericum perforatum*)
Hepatitis C direct acting antiviral	Elbasvir/grazoprevir
Lipid-modifying agents:	
HMG-CoA Reductase Inhibitors	Lovastatin, Simvastatin
Microsomal triglyceride transfer protein (MTTP) Inhibitor	Lomitapide
Long acting beta-adrenoceptor agonist	Salmeterol
PDE5 inhibitors	Sildenafil*, only when used for the treatment of pulmonary arterial hypertension (PAH)
	Avanafil
*see "**Section 4.3 and 4.4"** for co-administration of Sildenafil in patients with erectile dysfunction	

4.4 Special warnings and precautions for use

Antigout medicines

Life-threatening and fatal medicines interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir, as in **ALUVIA 100/25** .Concomitant admnistration with colchicine is contraindicated in patients with renal and/or hepatic impairment *(see* **Section 4.3 and Section 4.5**).

Anti-mycobacterials

Rifampicin: **ALUVIA 100/25** should not be co-administered with rifampicin because large decreases in lopinavir concentrations may significantly decrease the therapeutic effect (see **Section 4.5**).

Bedaquiline: Co-administration of bedaquiline with strong CYP3A4 inhibitors may increase the systemic exposure of bedaquiline, which could potentially increase the risk of bedaquiline-related adverse reactions (see **Section 4.5**). Bedaquiline must be used cautiously with **ALUVIA 100/25**, only if the benefit of co-administration outweighs the risk. Frequent monitoring of electrocardiogram and transaminases is recommended.

Delamanid: Co-administration of delamanid with a strong inhibitor of CYP3A (lopinavir/ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co administration of delamanid with **ALUVIA 100/25** is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **Section 4.5**).

Antipsychotics

Concomitant use of quetiapine with **ALUVIA 100/25** is contraindicated. Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities (**Section 4.5**).

Corticosteroids

Concomitant use of **ALUVIA 100/25** and inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone, or other glucocorticoids that are metabolised by CYP3A4, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

Concomitant use of **ALUVIA 100/25** 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 **ALUVIA 100/25** has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide or injectable triamcinolone.(see **Section 4.5**).

PDE5 Inhibitors

Co-administration of **ALUVIA 100/25** with avanafil is contraindicated. Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving **ALUVIA 100/25.** Co-administration of **ALUVIA 100/25** 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 **ALUVIA 100/25** is contra-indicated 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 **ALUVIA 100/25** 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 **Sections 4.3 and 4.5**).

HMG-CoA Reductase inhibitors

Concomitant use of **ALUVIA 100/25** with lovastatin or simvastatin is contra-indicated (see **Section 4.3**).Caution should be exercised if HIV protease inhibitors, including **ALUVIA 100/25** , are used concurrently with rosuvastatin or with other HMG-CoA reductase inhibitors

that are metabolised by the CYP3A4 pathway (e.g. atorvastatin), as this may increase the potential for serious reactions such as myopathy, including rhabdomyolysis (see **Section 4.5).**

Tipranavir

In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, tipranavir (500 mg twice daily) with ritonavir (200 mg twice daily), co-administered with lopinavir/ritonavir (400/100 mg twice daily), resulted in a 55 % and 70 % reduction in lopinavir AUC and C_{min} respectively. The concomitant administration of **ALUVIA 100/25** and tipranavir with low dose ritonavir is therefore not recommended.

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 **Aluvia 100/25**. 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. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor **ALUVIA 100/25** therapy and these events has not been established. Consideration should be given to the monitoring of blood glucose.

Pancreatitis

Pancreatitis has been observed in patients receiving lopinavir/ritonavir therapy, such as contained in **ALUVIA 100/25** including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to lopinavir/ritonavir has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **Section 4.4**). Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during **ALUVIA 100/25** therapy.

Hepatic Impairment

ALUVIA 100/25 is principally metabolised by the liver. Therefore, caution should be exercised when administering this medicine to patients with impaired hepatic function. **ALUVIA 100/25** 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 **ALUVIA 100/25** 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 **ALUVIA 100/25** in conjunction with other antiretroviral medicines.

In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with **ALUVIA 100/25** therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of **ALUVIA 100/25** treatment.

Resistance/*Cross-Resistance*

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of **ALUVIA 100/25** therap*y* on the efficacy of subsequently administered protease inhibitor is unknown.

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 **ALUVIA 100/25**. In some patient's additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors such as **ALUVIA 100/25** was continued or reintroduced. Neither a causal relationship nor a mechanism of action between protease inhibitor therapy and these events has been established.

PR Interval Prolongation

Lopinavir/ritonavir, such as contained in **ALUVIA 100/25** has been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Rare reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicines known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. **ALUVIA 100/25** should be used with caution in such patients (see **Section 5**).

Lipid Elevations

Treatment with lopinavir/ritonavir as contained in **ALUVIA 100/25** has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating **ALUVIA 100/25** 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 **ALUVIA 100/25** and HMG-CoA reductase inhibitors.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including lopinavir/ritonavir such as contained in **ALUVIA 100/25**. 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 tuberculosis,

Mycobacterium avium infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia,), 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 aetiology 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.

Use in the elderly

Clinical studies of lopinavir/ritonavir such as contained in **ALUVIA 100/25** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of **ALUVIA 100/25** 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 **ALUVIA 100/25** in paediatric patients below the age of six months have not been established. In HIV-infected patients age six months to 18 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. **ALUVIA 100/25** should not be administered once daily in pediatric patients.

4.5 Interaction with other medicines and other forms of interaction

ALUVIA 100/25 is a potent inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo.* Co-administration of **ALUVIA 100/25** and medicines primarily metabolised by CYP3A (e.g. dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors) may result in increased plasma concentrations of the other medicines that could increase or prolong their therapeutic and adverse effects (see **Section 4.4)**. 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 **ALUVIA 100/25**. Medicines that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in **TABLE 1** under **CONTRA-INDICATIONS**.

ALUVIA 100/25 is metabolised by CYP3A. Co-administration of **ALUVIA 100/25** and medicines that induce CYP3A may decrease lopinavir plasma concentrations and reduce

its therapeutic effect. Although not noted with concurrent ketoconazole, co-administration of **ALUVIA 100/25** and other medicines that inhibit CYP3A may increase lopinavir plasma concentrations.

These examples are a guide and not considered a comprehensive list of all possible medicines that may interact with ALUVIA 100/25 . The healthcare practitioner 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 **ALUVIA 100/25** was given alone or in combination with stavudine and lamivudine.

Didanosine

It is recommended that didanosine be administered on an empty stomach; therefore, didanosine may be co-administered with **ALUVIA 100/25** tablets without food.

Zidovudine and Abacavir

ALUVIA 100/25 induces glucoronidation, therefore **ALUVIA 100/25** has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Tenofovir

A study has shown that **ALUVIA 100/25** increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving **ALUVIA 100/25** and tenofovir should be monitored for tenofovir-associated adverse events.

All anti-HIV medicines

Increased creatinine phosphokinase (CPK), myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitor's such as **Aluvia 100/25,** particularly in combination with NRTIs.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine

No change in the pharmacokinetics of lopinavir was apparent in healthy adult subjects during nevirapine and **ALUVIA 100/25** 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 interaction is unknown. For patients with extensive protease inhibitor experience, phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase of lopinavir/ritonavir oral solution to 533/133 mg or lopinavir/ritonavir 500/125 mg twice daily should be considered when co-administered with nevirapine.

ALUVIA 100/25 should not be administered once daily in combination with nevirapine.

Efavirenz

When used in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in multiple protease inhibitor-experienced subjects, increasing the dose of lopinavir/ritonavir 25 % from 400/100 mg (two (2) 200/50 mg tablets) BID (twice daily) to 500/125 mg (two (2) 200/50 tablets + one (1) 100/25 mg tablet) yielded similar lopinavir plasma concentrations as compared to historical data of lopinavir/ritonavir 400/100 mg BID. For patients with extensive protease inhibitor experience, phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase of lopinavir/ritonavir oral solution to 533/133 mg or lopinavir/ritonavir 500/125 mg twice daily should be considered when co- administered with efavirenz.

Increasing the dose of **ALUVIA 100/25** tablets to 500/125 twice a day resulted in similar lopinavir plasma concentrations compared to lopinavir/ritonavir tablets 400/100 mg twice daily without efavirenz (see **Section 4.2**).

Increasing the dose of **ALUVIA 100/25** tablets to 600/150 (three (3) tablets) twice a day co-administered with efavirenz significantly increased the lopinavir plasma concentrations approximately 36 % and ritonavir concentrations approximately 56 % to 92 % compared to **ALUVIA 100/25** tablets 400/100 mg twice a day without efavirenz (see **Section 4.2**).

NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination

with **ALUVIA 100/25**.**ALUVIA 100/25** should not be administered once daily in combination with efavirenz. (*see **Section 5**).*

Delavirdine

Delavirdine has the potential to increase plasma concentrations of lopinavir.

Etravirine

Concomitant use of **ALUVIA 100/25** with etravirine causes a decrease in the plasma concentrations of etravirine, but no dose adjustment is required. Refer to the etravirine prescribing professional information.

Rilpivirine

Concomitant use of **ALUVIA 100/25** with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required. *Refer to the rilpivirine prescribing professional information.*

Protease Inhibitors (PIs)

Amprenavir

ALUVIA 100/25 is expected to increase concentrations of amprenavir (amprenavir 750 mg BID plus lopinavir/ritonavir produces increased AUC, similar C_{max}, increased C_{min}, relative to amprenavir 1200 mg BID).

Co-administration of **ALUVIA 100/25** and amprenavir result in decreased concentrations of lopinavir (see **Section 4.2**). The dose of **ALUVIA 100/25** may need to be increased

during co-administration of amprenavir, particularly in patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir.

ALUVIA 100/25 should not be administered once daily in combination with amprenavir.

Fosamprenavir

A study has shown that co-administration of lopinavir/ritonavir, such as contained in **ALUVIA 100/25** with fosamprenavir lowers amprenavir and lopinavir concentrations. Appropriate doses of the combination of fosamprenavir and **ALUVIA 100/25** with respect to safety and efficacy have not been established.

Indinavir

ALUVIA 100/25 is expected to increase concentrations of indinavir (indinavir 600 mg BID plus lopinavir/ritonavir produces similar AUC, decreased C_{max}, increased C_{min} relative to indinavir 800 mg TID). The dose of indinavir may need to be decreased during co-administration of **ALUVIA 100/25** 400/100 mg BID. **ALUVIA 100/25** once daily has not been studied in combination with indinavir.

Nelfinavir

ALUVIA 100/25 is expected to increase concentrations of nelfinavir and increased M8 metabolite of nelfinavir (nelfinavir 1000 mg BID plus lopinavir/ritonavir produces similar AUC, similar C_{max}, increased C_{min} relative to nelfinavir 1250 mg BID). Co-administration of **ALUVIA 100/25** and nelfinavir result in decreased concentrations of lopinavir (see Section 4.2). The dose of lopinavir/ritonavir may need to be increased when co-administered with

nelfinavir, particularly in HIV patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir. **(Section 4.2 and 5)**. **ALUVIA 100/25** should not be administered once daily in combination with nelfinavir.

Ritonavir

When lopinavir/ritonavir, as contained in **ALUVIA 100/25,** was co-administered with an additional 100 mg ritonavir twice daily, lopinavir AUC increased 33 % and C_{min} increased 64 % as compared to another lopinavir/ritonavir formulation, 400/100 mg administered twice daily. *(see **Section 5**).*

Saquinavir

ALUVIA 100/25 is expected to increase concentrations of saquinavir (saquinavir 800 mg BID plus lopinavir/ritonavir produces increased AUC, increase C_{max}, increased C_{min} relative to saquinavir 1200 mg TID). The dose of saquinavir may need to be decreased when co-administered with **ALUVIA 100/25** BID. **ALUVIA 100/25** once daily has not been studied in combination with saquinavir *(see* **Section 5***).*

Hepatitis C direct acting antivirals

Boceprevir

Concomitant administration of boceprevir and **ALUVIA 100/25** resulted in reduced boceprevir and lopinavir steady-state exposure. It is not recommended to co-administer **ALUVIA 100/25** and boceprevir.

Glecaprevir/pibrentasvir

Concomitant administration of glecaprevir/pibrentasvir and **ALUVIA 100/25** is not reccommended 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 **ALUVIA 100/25** therefore, co-administration is not recommended.

Simeprevir

Concomitant use of **ALUVIA 100/25** and simeprevir may result in increased plasma concentrations of simeprevir. It is not recommended to co-administer **ALUVIA 100/25**, and simeprevir.

Sofosbuvir/velpatasvir/voxilaprevir

Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and **ALUVIA 100/25** is not recommended due to the potential for increased toxicity, which may negatively impact compliance.

Telaprevir

Concomitant administration of telaprevir and **ALUVIA 100/25** resulted in reduced telaprevir steady-state exposure, while the lopinavir steadystate exposure was not affected.

HIV CCR5 – antagonist

Maraviroc: Concurrent administration of maraviroc with **ALUVIA 100/25** will increase plasma levels of maraviroc. The dose of maraviroc should be decreased during co-administration with lopinavir/ritonavir 400/100 mg BID. For further details, see complete professional information for maraviroc.

OTHER MEDICINES

Analgesics

Fentanyl: **ALUVIA 100/25** 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 **ALUVIA 100/25.**

Antidysrhythmics

Amiodarone, Bepridil, Dronedarone, Systemic Lidocaine, Lignocaine (Lidnocaine) and Quinidine: Concentrations may be increased when co-administered with **ALUVIA 100/25.** 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 **ALUVIA 100/25** with digoxin, with appropriate monitoring of serum digoxin levels.

Anticancer Medicines

Abemaciclib ,apalutamide , dasatinib ,encorafenib , ibrutinib ,ivosidenib , neratinib , nilotinib , venetoclax, vincristine, vinblastine: May have their serum concentrations increased when co-administered with **ALUVIA 100/25** resulting in the potential for increased adverse events , some of which may be serious. Co-administration of venetoclax or ibrutinib with lopinavir/ritonavir could increase venetoclax or ibrutinib exposure potentially resulting in a serious risk of tumor lysis syndrome. Coadministration of encorafenib or ivosidenib with **ALUVIA 100/25** 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 professional information for dosing instructions.

Coadministration of apalutamide is contraindicated with **ALUVIA 100/25** since apalutamide may decrease exposure of **ALUVIA 100/25** with potential loss of virologic response. In addition, co-administration of apalutamide and **ALUVIA 100/25** may lead to increased exposure of apalutamide resulting in increased potential for adverse events including seizure.

Anticoagulants

Warfarin: Warfarin concentrations may be affected when co-administered with **ALUVIA 100/25.** It is recommended that INR (international normalised ratio) be monitored.

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

Antidepressants

Bupropion: Concurrent administration of bupropion with **ALUVIA 100/25** 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 **ALUVIA 100/25**, the combination should be used with caution and a lower dose of trazodone should be considered.

Anticonvulsants

Phenobarbital, Phenytoin, Carbamazepine: These medicines are known to induce CYP3A4 and may decrease lopinavir concentrations. **ALUVIA 100/25** should not be administered once daily in combination with phenobarbital, phenytoin or carbamazepine.

In addition, co-administration of phenytoin and lopinavir/ritonavir resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administration with **ALUVIA 100/25.**

Lamotrigine and valproate: Co-administration of **ALUVIA 100/25** 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 **ALUVIA 100/25** and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments *(*see **Section 5)**.

Antifungals

Ketoconazole and Itraconazole: Ketoconazole and itraconazole may have their serum concentrations increased by **ALUVIA 100/25.** High doses of ketoconazole and itraconazole (greater than 200 mg/day) are not recommended.

Voriconazole: A study has shown that co-administration of ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39 %; therefore, co-administration of **ALUVIA 100/25** and voriconazole should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Antigout medicines

Concentrations of colchicine are expected to increase when co-administered with **ALUVIA 100/25**. Life-threatening and fatal medicine interactions have been reported in patients treated with colchicine and ritonavir. Concomitant admnistration with colchicine is contraindicated in patients with renal and/or hepatic impairment. Refer to the colchicine professional information for prescribing information. (see **Section 4.3 and 4.4**).

Anti-infectives

Clarithromycin: Moderate increases in clarithromycin AUC are expected when co-administered with **ALUVIA 100/25**. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered.

Anti-mycobacterials

Rifabutin: When rifabutin and lopinavir/ritonavir, such as contained in **ALUVIA 100/25** were co-administered for ten days, rifabutin (parent drug and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3,5- and 5,7-fold, respectively. On the basis of these data, a rifabutin dose reduction of 75 % (i.e. 150 mg every other day or three times per week) is recommended when administered with **ALUVIA 100/25.** Further dose reduction of rifabutin may be necessary.

Rifampicin: Due to large decreases in lopinavir concentrations, rifampicin should not be used in combination with **ALUVIA 100/25 (**see **Section 4.4**). The use of rifampicin with standard dose **ALUVIA 100/25** may lead to loss of virologic response and possible resistance to **ALUVIA 100/25** or to the class of protease inhibitors or other co-administered antiretroviral medicines. Co-administration of rifampicin with 800/200 mg lopinavir/ritonavir BID resulted in decreases in lopinavir of up to 57 % and with lopinavir/ritonavir 400/400 mg BID resulted in decreases of up to 7 % when compared to lopinavir/ritonavir 400/100 mg BID dosed in the absence of rifampicin. ALT and AST elevations have been noted in studies with higher doses of lopinavir/ritonavir co-administered with rifampicin and may be dependent on the sequence of dose administration. If co-administration is being considered, **ALUVIA 100/25** should be initiated at standard dose for approximately 10 days prior to addition of rifampicin. **ALUVIA 100/25** dose should then be titrated upward. Close monitoring of liver function is indicated.

Bedaquiline: In a healthy volunteer medicine interaction study of 400 mg single dose bedaquiline and lopinavir/ritonavir 400/100 mg twice daily for 24 days, bedaquiline exposures (AUC) were increased by 22%. Bedaquiline must be used cautiously with **ALUVIA 100/25**, only if the benefit of co**-**administration outweighs the risk. More frequent monitoring of electrocardiogram and transaminases is recommended. (see **Section 4.4).**

Delamanid: In a healthy volunteer medicine interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, 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 **ALUVIA 100/25** is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **Section 4.4)**.

Antiparasitics

Atovaquone: Decreases in the therapeutic concentration of atovaquone are possible when co-administered with **ALUVIA 100/25**. Increases in atovaquone doses may be necessary.

Antipsychotics

Quetiapine: Due to CYP3A inhibition by **ALUVIA 100/25** concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities.

Corticosteroids

Dexamethasone: Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations.

Inhaled, injectable, or intranasal fluticasone propionate, budesonide, triamcinolone: Concomitant use of lopinavir/ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4, such as budesonide and triamcinolone is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

Consider alternatives to fluticasone propionate, budesonide and injectable triamcinolone particularly for long-term use (see **Section 4.4)**.

Dihydropyridine Calcium Channel Blockers

Felodipine, Nifedipine, Nicardipine etc.: May have their serum concentrations increased by **ALUVIA 100/25.**

PDE5 inhibitors

Avanafil: Co-administration of **ALUVIA 100/25** with avanafil is expected to result in large increases in Avanafil exposure and is contraindicated (see **Section 4.3)**.

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 (see **Section 4.4)**.

Concomitant use of sildenafil with **ALUVIA 100/25** is contraindicated in pulmonary arterial hypertension (PAH) patients (see **Section 4.3**).

Tadalafil: Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events (see **Section 4.4).** When tadalafil is administered for the treatment of pulmonary arterial hypertension to patients who are receiving lopinavir/ritonavir, 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 (see **Section 4.4).**

GnRH Receptor Antagonists

Elagolix: Coadministration of elagolix with **ALUVIA 100/25** could increase elagolix exposure through inhibition of OATP, CYP 3A, and P-gp. Known serious adverse events for elagolix include suicidal ideation and hepatic transaminase elevations. In addition, elagolix is a weak/moderate inducer of CYP3A, which may decrease exposure of lopinavir/ritonavir. Refer to the elagolix professional information for dosing information with strong CYP-3A4 inhibitors.

Kinase Inhibitors (also see anticancer medicines above)

Fostamatinib: Coadministration of fostamatinib with **ALUVIA 100/25** could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia.

Herbal Products

St. John's Wort: Patients on **ALUVIA 100/25** should not use products containing St. John's Wort concomitantly, since this combination may be expected to result in reduced plasma concentrations of **ALUVIA 100/25**. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see **Section 4.3 and 4.4**).

HMG-CoA Reductase Inhibitors

Lovastatin and *Simvastatin:* HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with **ALUVIA 100/25**. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicines with **ALUVIA 100/25** is contra-indicated (see **Section 4.3).**

Atorvastatin: Atorvastatin is less dependent on CYP3A for metabolism. When atorvastatin was given concurrently with **ALUVIA 100/25** a mean 4.7-fold and 5.9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with **ALUVIA 100/25**, the lowest possible doses of atorvastatin should be administered (see **Section 4.4**).

Pravastatin and Fluvastatin: Results from a medicine interaction study with **ALUVIA 100/25** and pravastatin reveal no clinically significant interaction. The metabolism of pravastatin

and fluvastatin is not dependent on CYP3A4, and interactions are not expected with **ALUVIA 100/25.** If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Lomitapide: Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27- fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated. (see **Section 4.3**)

Immunosuppressants

Ciclosporin, Tacrolimus and Sirolimus (rapamycin) etc.: Concentrations of these medicines may be increased when co-administered with **ALUVIA 100/25**. More frequent therapeutic concentration monitoring is recommended until blood levels of these products have stabilised.

Methadone

ALUVIA 100/25 was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Oral Contraceptives or Patch Contraceptives

Since levels of ethinyl estradiol may be decreased, alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives or patch contraceptives and **ALUVIA 100/25** are co-administered.

Vasodilating medicines:

*Bosentan: C*oadministration of bosentan and **ALUVIA 100/25** increased steady-state, bosentan maximum concentrations (C_{max}) and area-under the-curve (AUC) by 6-fold and 5-fold, respectively. Refer to the bosentan professional information for prescribing information.

Clinically Significant Medicine Interactions Not Expected

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

Based on known metabolic profiles, clinically significant medicine interactions are not expected between **ALUVIA 100/25** and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, or fluconazole in patients with normal renal and hepatic function.

Clinical studies showed no clinically significant **i**nteraction between lopinavir/ritonavir and raltegravir.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **ALUVIA 100/25** in pregnant women has not been established.

Human Data

Risk Summary

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

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 lopinavir/ritonavir in the first trimester.

Breastfeeding

HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV and the potential for serious adverse reactions in breastfeeding infants, if they are receiving **ALUVIA 100/25**.

Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk.

4.7 Effect on the 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 **ALUVIA 100/25.**

4.8 Undesirable effects

a. Summary of the safety profile

Adults

Treatment-Emergent Adverse reaction

The safety of **ALUVIA 100/25** 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 (8 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies lopinavir/ritonavir was used in combination with efavirenz or nevirapine.

Commonly reported adverse reactions to lopinavir/ritonavir included diarrhoea, nausea~~,~~ and vomiting~~,~~ vomiting may occur at the beginning of the treatment while hypertriglyceridaemia and hypercholesterolaemia may occur later.

b. Tabulated list of adverse reactions

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); uncommon (≥1/1000, <1/100); rare (≥ 1/10 000, < 1/1000) and very rare (≤ 1/10 000)

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 reactivation syndrome
Endocrine disorders	Uncommon	Hypogonadism
Metabolic and nutritional disorders	common	hypercholesterolaemia, hypertriglyceridaemia lactic acidosis, blood glucose disorders including diabetes mellitus, hyperglycaemia, decreased appetite,
	uncommon	Weight increased, increased appetite
Psychiatric disorders	Common	anxiety
	Uncommon	Abnormal dreams, decreased libido

Undesirable Effects in Clinical Studies in Adult Patients		
Nervous System disorders	Common	Headache (including migraine), neuropathy including (peripheral neuropathy), dizziness, insomnia
	Uncommon	Cerebrovascular accident, convulsion, tremor, ageusia, dysgeusia
Eye disorders	Uncommon	visual 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	Deep thrombophlebitis, vasodilatation
Gastrointestinal disorders	Very common	Diarrhoea, nausea
	Common	pancreatitis vomiting, gastroesophageal reflux disease, gastroenteritis and colitis abdominal pain (upper and lower), abdominal distension, dyspepsia, haemorrhoids, flatulence

Undesirable Effects in Clinical Studies in Adult Patients		
	Uncommon	gastrointestinal haemorrhage including gastrointestinal ulcer duodenitis, gastric ulcer, gastritis, mouth ulcerations, rectal haemorrhage, stomatitis, faecal incontinence, constipation, dry mouth
Hepatobiliary disorders	Common Uncommon Very rare	Hepatitis including AST, ALT and GGT increases hepatomegaly, hepatic steatosis, cholangitis, hyperbilirubinaemia Jaundice
Skin and subcutaneous tissue	Common Uncommon Very rare	Rash including maculopapular rash, dermatitis/rash including eczema and seborrheic dermatitis, night sweats, pruritus, Alopecia, capillaritis, vasculitis Stevens-johnson syndrome, erythema multiforme
Musculoskeletal and connective	Common	Myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such as weakness and spasms

Undesirable Effects in Clinical Studies in Adult Patients		
tissue disorders	Uncommon	Rhabdomyolysis, osteonecrosis
Renal and urinary disorders	Uncommon	creatinine clearance decreased, nephritis, haematuria
Reproductive system and breast disorders	Common	Erectile dysfunction, menstrual disorders- amenorrhoea, menorrhagia
General disorders and administration site conditions	Common	Fatigue including asthenia

Post-marketing Experience

Hepatobiliary disorders: Hepatitis has been reported in patients on lopinavir/ritonavir therapy, very similar to that of **ALUVIA 100/25.**

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

Cardiac disorders: Bradydysrhythmia has been reported.

Renal and urinary disorders: Nephrolithiasis.

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy including lopinavir/ritonavir with Grade 3 to 4 laboratory abnormalities are presented in **TABLE 2** and **TABLE 3**

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

		Study 863 (48 Weeks)		Study 418 (48 weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	Limit[1]	Lopinavir/ ritonavir 400/100 mg BID + d4t + 3TC (n=326)	Nelfinavir 750 mg TID + d4T + 3TC (n=327)	Lopinavir/ ritonavir 800/200 mg QD + TDF + FTC (n=115)	Lopinavir/ ritonavir 400/100 mg BID + TDF + FTC (n=75)	Lopinavir/ ritonavir BID + d4T + 3TC (n=100)	Lopinavir/ritonavir QD + TDF + FTC (n=333)	Lopinavir/ritonavir BID + TDF + FTC (n=331)
Chemistry	**High**							
Glucose	>13,8 mmol/L	2 %	2 %	3%	1 %	4 %	0 %	< 1 %
Uric Acid	>0,71 mmol/L	2 %	2 %	0 %	3 %	5 %	< 1 %	1 %
Total Bilirubin	>59,5 micromol/L	<1 %	0 %	0 %	0 %	1 %		

		Study 863 (48 Weeks)		Study 418 (48 weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	Limit[1]	Lopinavir/ ritonavir 400/100 mg BID + d4t + 3TC (n=326)	Nelfinavir 750 mg TID + d4T + 3TC (n=327)	Lopinavir/ ritonavir 800/200 mg QD + TDF + FTC (n=115)	Lopinavir/ ritonavir 400/100 mg BID + TDF + FTC (n=75)	Lopinavir/ ritonavir BID + d4T + 3TC (n=100)	Lopinavir/ritonavir QD + TDF + FTC (n=333)	Lopinavir/ritonavir BID + TDF + FTC (n=331)
AST	>180 U/L	2 %	4 %	5 %	3 %	10 %	1 %	2 %
ALT	>215 U/L	4 %	4 %	4 %	3 %	11 %	1 %	1 %
GGT	>300 U/L	N/A	N/A	N/A	N/A	10 %	N/A	N/A
Total Cholesterol	>7,77 mmol/L	9 %	5 %	3 %	3 %	27 %	N/A	N/A
Triglyceride	>8,25 mmol/L	9 %	1 %	5 %	4 %	29 %	3 %	6 %
Amylase	>2 x ULN	3 %	2 %	7 %	5 %	4 %	N/A	N/A
Lipase	>2 x ULN	N/A	N/A	N/A	N/A	N/A	3 %	5 %
Chemistry	**Low**							

		Study 863 (48 Weeks)		Study 418 (48 weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	Limit[1]	Lopinavir/ ritonavir 400/100 mg BID + d4t + 3TC (n=326)	Nelfinavir 750 mg TID + d4T + 3TC (n=327)	Lopinavir/ ritonavir 800/200 mg QD + TDF + FTC (n=115)	Lopinavir/ ritonavir 400/100 mg BID + TDF + FTC (n=75)	Lopinavir/ ritonavir BID + d4T + 3TC (n=100)	Lopinavir/ritonavir QD + TDF + FTC (n=333)	Lopinavir/ritonavir BID + TDF + FTC (n=331)
Calculated Creatinine Clearance	< 50 mL/min	N/A	N/A	N/A	N/A	N/A	2 %	2 %
Haematology	**Low**							
Neutrophils	0,75 x 10^9/L	1 %	3 %	5 %	1 %	5 %	2 %	1 %

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

[2] Criterion for study 730 was >5x ULN (AST/ALT)

TABLE 3: Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2 % of Adult Protease Inhibitor-Experienced Patients

		Study 888 (48 weeks)			Study 957[2] and Study 765[3] (84 – 144 Weeks)	Study 802 (48 weeks)	
Variable	Limit[1]	Lopinavir/ritonavir 400/100 mg BID + NVP + NRTIs (n=148)	Investigator selected PI(s) + NVP + NRTIs (n=140)		Lopinavir/ritonavir BID + NNRTI + NRTIs (n=127)	Lopinavir/ritonavir 800/200 mg Once Daily + NRTIs (n=300)	Lopinavir/ritonavir 400/100 mg Twice daily + NRTIs (n=299)
Chemistry	**High**						
Glucose	>13,8 mmol/L	1 %	2 %		5 %	2 %	2 %
Uric Acid	>0,71 mmol/L	0 %	1 %		1 %		
Total Bilirubin	>59,5 µmol/L	1 %	3 %		1 %	1 %	1 %
AST	>180 U/L	5 %	11 %		8 %	3 %	2 %
ALT	>215 U/L	6 %	13 %		10 %	2 %	2 %

		Study 888 (48 weeks)			Study 957[2] and Study 765[3] (84 – 144 Weeks)	Study 802 (48 weeks)	
Variable	Limit[1]	Lopinavir/ritonavir 400/100 mg BID + NVP + NRTIs (n=148)	Investigator selected PI(s) + NVP + NRTIs (n=140)		Lopinavir/ritonavir BID + NNRTI + NRTIs (n=127)	Lopinavir/ritonavir 800/200 mg Once Daily + NRTIs (n=300)	Lopinavir/ritonavir 400/100 mg Twice daily + NRTIs (n=299)
GGT	>300 U/L	N/A	N/A		29 %	N/A	N/A
Total Cholesterol	>7,77 mmol/L	20 %	21 %		39 %	6 %	7 %
Triglyceride	>8,25 mmol/L	25 %	21 %		36 %	5 %	6 %
Amylase	>2 x ULN	4 %	8 %		8 %	4 %	4 %
Lipase	>2 x ULN	N/A	N/A		N/A	4 %	1 %
Creatine Phosphokinase	>4 x ULN	N/A	N/A		N/A	4 %	5 %
Chemistry	**Low**						

		Study 888 (48 weeks)			Study 957[2] and Study 765[3] (84 – 144 Weeks)	Study 802 (48 weeks)	
Variable	Limit[1]	Lopinavir/ritonavir 400/100 mg BID + NVP + NRTIs (n=148)	Investigator selected PI(s) + NVP + NRTIs (n=140)		Lopinavir/ritonavir BID + NNRTI + NRTIs (n=127)	Lopinavir/ritonavir 800/200 mg Once Daily + NRTIs (n=300)	Lopinavir/ritonavir 400/100 mg Twice daily + NRTIs (n=299)
Calculated Creatinine Clearance	< 50 ml/min	N/A	N/A		N/A	3 %	3 %
Inorganic Phosphorus	< 0,48 mmol/L	1 %	0 %		2 %	1 %	<1 %
Haematology	**Low**						
Neutrophils	0,75 x 10^9/L	1 %	2 %		4 %	3 %	4 %
Haemoglobin	< 80 g/L	1 %	1 %		1 %	1 %	2 %

		Study 888 (48 weeks)			Study 957[2] and Study 765[3] (84 – 144 Weeks)	Study 802 (48 weeks)	
Variable	Limit[1]	Lopinavir/ritonavir 400/100 mg BID + NVP + NRTIs (n=148)	Investigator selected PI(s) + NVP + NRTIs (n=140)		Lopinavir/ritonavir BID + NNRTI + NRTIs (n=127)	Lopinavir/ritonavir 800/200 mg Once Daily + NRTIs (n=300)	Lopinavir/ritonavir 400/100 mg Twice daily + NRTIs (n=299)

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

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

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

[4] Criterion for Study 802 was >5x ULN (AST/ALT)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: 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

Human experience of acute overdosage with **ALUVIA 100/25** is limited. Treatment of overdose with **ALUVIA 100/25** should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

There is no specific antidote for overdose with **ALUVIA 100/25**. If indicated, elimination of unabsorbed medicine should be achieved by emesis or gastric lavage.

Administration of activated charcoal may also be used to aid in removal of unabsorbed medicine. Since **ALUVIA 100/25** is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A20.2.8 - Antiviral agent

Mechanism of action

Lopinavir/ritonavir tablets are 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 tablets, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. Lopinavir prevents cleavage of the *gag-pol* polyprotein, resulting in the production of immature, non-infectious virus.

Antiviral activity in vitro

The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50 % effective concentrate (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10 to 27 nM (0,006 to 0,017 micrograms/mL, 1 micrograms/mL equals 1,6 microM) and ranged from 4 to 11 nM (0,003 to 0,007 micrograms/mL) against several HIV-1 clinical isolates (n = 6). In the presence of 50 % human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 to 289 nM (0,04 to 0,18 micrograms/mL) representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance

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

Cross-Resistance – Pre-clinical Studies

Varying degrees of cross-resistance have been observed among protease inhibitors. The *in vitro* activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined.

Isolates that displayed greater than 4-fold reduced susceptibility to nelfinavir (n = 13) and saquinavir (n = 4), displayed less than 4-fold reduced susceptibility to lopinavir. Isolates with greater than 4-fold reduced susceptibility to indinavir (n = 16) and ritonavir (n = 3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir.

Cross-Resistance – During Lopinavir/Ritonavir Therapy

Little information is available on the cross-resistance of viruses selected during therapy with lopinavir/ritonavir. Isolates from four patients previously treated with one or more protease inhibitors (PI's) that developed increased lopinavir phenotypic resistance during lopinavir/ritonavir therapy either remained cross-resistant or developed cross-resistance to ritonavir, indinavir and nelfinavir. All rebound viruses either remained fully sensitive or

demonstrated modestly reduced susceptibility to amprenavir (up to 8,5-fold concurrent with 99-fold resistance to lopinavir). The rebound isolates from the two subjects with no prior saquinavir treatment remained fully sensitive to saquinavir.

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

Virologic response to lopinavir/ritonavir has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T and I84V.

TABLE 4 shows the 48-week virologic response (HIV RNA <400 copies/mL) according to the number of the above protease inhibitor resistance mutations at baseline in studies 888 and 765 and study 957.

TABLE 4: Virologic Response (HIV RNA <400 copies/mL) at Week 48 by Baseline Lopinavir/ritonavir Susceptibility and by Number of Protease Substitutions Associated with Reduced Response to Lopinavir/ritonavir[1]

Number of protease inhibitor mutations at baseline[1]	**Study 888 (Single protease inhibitor-experienced[2]**	**Study 765 (Single protease inhibitor-experienced[3]**	**Study 957 (Multiple protease inhibitor-experienced[4]**

	NNRTI-naïve) (n=130)	**NNRTI–naïve) (n=56)**	**NNRTI-naïve) (n=50)**
0 – 2	76/103 (74 %)	34/45 (76 %)	19/20 (95 %)
3 – 5	13/26 (50 %)	8/11 (73 %)	18/26 (69 %)
6 or more	0/1 (0 %)	N/A	1/4 (25 %)

1 Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

2 43 % indinavir, 42 % nelfinavir, 10 % ritonavir, 15 % saquinavir.

3 41 % indinavir, 38 % nelfinavir, 4 % ritonavir, 16 % saquinavir.

4 86 % indinavir, 54 % nelfinavir, 80 % ritonavir, 70 % saquinavir.

TABLE 5: Virologic Response (HIV-1 RNA <50 copies/mL) at Week 48 by Baseline Number of Protease Substitutions Associated with Reduced Response to Lopinavir/ritonavir

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

1 Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

2 88 % NNRTI-experienced, 47 % PI-experienced (24 % nelfinavir, 19 % indinavir, 13 % atazanavir)

3 81 % NNRTI-experienced, 45 % PI-experienced (20 % nelfinavir, 17 % indinavir, 13 % atazanavir)

5.2 Pharmacokinetic properties

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir.

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

Absorption

In a pharmacokinetic study in HIV-positive subjects (n = 18), multiple dosing with 400/100 mg lopinavir/ritonavir twice daily with food for three weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 12,3 ± 5,4 micrograms/mL, occurring approximately four hours after administration.

The mean steady-state trough concentration prior to the morning dose was 8,1 ± 5,7 micrograms/mL and minimum concentration within a dosing interval was 5,6 ± 4,5 micrograms/mL. Lopinavir AUC over a 12-hour dosing interval averaged 113,2 ± 60,5

micrograms•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of Food on Oral Absorption

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

Lopinavir/ritonavir tablets have also shown less pharmacokinetic variability under all meal conditions.

Distribution

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

Biotransformation:

In vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent

CYP3A inhibitor, which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir.

A ^{14}C-lopinavir study in humans showed that 89 % of the plasma radioactivity after a single 400/100 mg lopinavir/ritonavir dose was due to parent compound. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 to 16 days.

Elimination

Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10,4 ± 2,3 % and 82,6 ± 2,5 % of an administered dose of ^{14}C-lopinavir can be accounted for in urine and faeces, respectively, after eight days. Unchanged lopinavir accounted for approximately 2,2 and 19,8 % of the administered dose in urine and faeces, respectively. After multiple dosing, less than 3 % of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5,98 ± 5,75 L/hr (mean ± SD, N = 19).

Once Daily Dosing

The pharmacokinetics of once daily lopinavir/ritonavir has 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 24 weeks without meal restriction (n = 16) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 14,8 ±.5 microgram/mL, occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 5,5 ± 5,4 microgram/mL and minimum concentration within a dosing interval was 3,2 ± 3,4 microgram/mL.

Lopinavir AUC over a 24-hour dosing interval averaged 206,5 ± 89,7 microgram•h/mL.

Effects on Electrocardiogram

QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once-daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95 % upper confidence bound) differences in QTcF from placebo were 3,6 (6,3) msec and 13,1 (15,8) msec for 400/100 mg twice-daily and supratherapeutic 800/200 mg twice daily lopinavir/ritonavir, respectively. The two regimens resulted in exposures on Day 3 that were approximately 1,5 and 3-fold higher than those observed with recommended once-daily or twice-daily lopinavir/ritonavir doses at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec. Modest prolongation of the PR interval was also noted in subjects. Receiving lopinavir/ritonavir in the same study on Day 3. Maximum PR interval was 286 msec and no second- or third-degree heart block was observed (see **Section 4.4**).

Special Populations

Gender, Ethinicity and Age

Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to ethnicity have been identified.

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**).

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 the 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 mcg•h/mL, 8,2 ± 2,9 and 3,4 ± 2,1 mcg/mL, respectively after lopinavir/ritonavir 230/57,5 mg/m^2 BID without nevirapine (n = 12), and were 85,8 ± 36,9 mcg•h/mL, 10,0 ± 3,3 and 3,6 ± 3,5 mcg/mL, respectively after 300/75 mg/m^2 BID with nevirapine (n = 12). The nevirapine regimen was 7 mg/kg BID (six months to eight years) or 4 mg/kg BID (greater than eight years).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Copovidone

Sorbitan laurate

Colloidal anhydrous silica

Sodium stearyl fumarate

Film-coating:

Polyvinyl alcohol

Titanium dioxide (E171)

Talc

Macrogols 3350

Iron ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store **ALUVIA 100/25** film-coated tablets at room temperature (below 25 °C).

Keep well closed. **KEEP OUT OF REACH OF CHILDREN.**

6.5 Nature and contents of container

ALUVIA 100/25 film-coated tablets are supplied in white High Density Polyethylene (HDPE) bottles closed with white propylene caps.

Each bottle contains 56 or 60 tablets.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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