SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

RILOVIA 100/25 (film-coated tablets)

RILOVIA 200/50 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RILOVIA 100/25:

Each film-coated tablet contains 100 mg lopinavir and 25 mg ritonavir.

Sugar free

RILOVIA 200/50:

Each film-coated tablet contains 200 mg lopinavir and 50 mg ritonavir.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

RILOVIA 100/25: Light yellow to yellow coloured, round, biconvex, film-coated tablets, debossed with "M172" on one side and plain on the other side.

RILOVIA 200/50: Light yellow to yellow coloured, film-coated ovaloid tablets, debossed with "M124" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RILOVIA 100/25 and **RILOVIA 200/50** are indicated for the treatment of HIV-1 infected adults, in combination with other antiretroviral medicines.

Most experience with lopinavir/ritonavir tablets is derived from the use of the medicine in antiretroviral therapy naïve patients. Data in heavily pretreated protease inhibitor experienced patients are limited.

There are limited data on salvage therapy on patients who have failed therapy with **RILOVIA 100/25** and **RILOVIA 200/50**.

4.2 Posology and method of administration

Posology

RILOVIA 100/25 and **RILOVIA 200/50** tablets should be prescribed by doctors who are experienced in the treatment of HIV infection.

RILOVIA (200 mg/50 mg)

Adult and adolescent use: The recommended dosage of **RILOVIA** is two 200/50 mg tablets twice daily taken with or without food.

Paediatric use (2 years of age and above): The adult dose of **RILOVIA 100/25** and **RILOVIA 200/50** (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.

The following table contains dosing guidelines for **RILOVIA** (100/25 mg) tablets based on BSA.

Paediatric Dosing Guidelines	
Body Surface Area (m^2)	**Recommended number of RILOVIA (100/25 mg) tablets twice-daily**
≥ 1,4	4 tablets (400/100 mg)

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

BSA (m^2) = √ (Height (cm) X Weight (kg) / 3600)

Concomitant therapy: Efavirenz or nevirapine

The following table contains dosing guidelines for **RILOVIA 100/25** and **RILOVIA 200/50** based on BSA when used in combination with efavirenz or nevirapine in children.

Paediatric Dosing Guidelines with concomitant efavirenz or nevirapine	
Body Surface Area (m^2)	**Recommended number of RILOVIA (100/25 mg) tablets twice-daily. The adequate dosing may be achieved with the two available strengths of lopinavir/ritonavir tablets: RILOVIA (100/25 mg)** and **RILOVIA (200/50 mg.)***
≥ 1,4	500/125 mg

* **RILOVIA 100/25** and **RILOVIA 200/50** tablets must not be chewed, broken or crushed.

Special populations

Hepatic impairment:

In HIV-infected patients with mild to moderate hepatic impairment, an increase of approximately 30 % in lopinavir exposure has been observed. No data are available in patients with severe hepatic impairment.

RILOVIA 100/25 and **RILOVIA 200/50** should not be given to these patients.

Renal impairment:

No dose adjustment is necessary in patients with renal impairment. Caution is warranted when **RILOVIA 100/25** and **RILOVIA 200/50** are used in patients with severe renal impairment.

Paediatric population

Children less than 2 years of age: **RILOVIA 100/25** and **RILOVIA 200/50** are not recommended for use in children below 2 years of age due to insufficient data on safety and efficacy.

Method of administration

RILOVIA 100/25 and **RILOVIA 200/50** film-coated tablets are administered orally and must be swallowed whole and not chewed, broken or crushed. **RILOVIA 100/25** and **RILOVIA 200/50** film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients in **RILOVIA 100/25** and **RILOVIA 200/50** tablets.

Patients with severe hepatic insufficiency.

RILOVIA 100/25 and **RILOVIA 200/50** contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. **RILOVIA 100/25** and **RILOVIA 200/50** should not be co-administered 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 the TABLE below.

MEDICINES WHICH SHOULD NOT BE CO-ADMINISTERED WITH RILOVIA 100/25 and **RILOVIA 200/50.**

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 medicines	St. John's Wort *(Hypericum perforatum)* (due to the risk of decreased plasma concentrations and reduced clinical effects of **RILOVIA 100/25** and **RILOVIA 200/50)**
Hepatitis C direct acting antiviral	Elbasvir/grazoprevir
Lipid-modifying agents: HMG-CoA Reductase Inhibitors Microsomal triglyceride transfer protein (MTTP) Inhibitor	Lovastatin, Simvastatin Lomitapide
Long acting beta-adrenoceptor agonist	Salmeterol
PDE5 inhibitors	Sildenafil*, only when used for the treatment of pulmonary arterial hypertension (PAH)
	Avanafil, vardenafil
*see "section 4.3 and section 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 medicine interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir, as in **RILOVIA 100/25** and **RILOVIA 200/50**. Concomitant administration with colchicine is contraindicated in patients with renal and/or hepatic impairment (see section 4.3 and section 4.5).

Anti-mycobacterials

Rifampicin: **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50**, 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 **RILOVIA 100/25** and **RILOVIA 200/50** is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.5).

Antipsychotics:

Concomitant use of quetiapine with **RILOVIA 100/25** and **RILOVIA 200/50** is contraindicated. Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities (see section 4.5).

Corticosteroids:

Concomitant use of **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** have been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide or injectable triamcinolone (see section 4.5).

PDE5 Inhibitors:

Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** with avanafil is contraindicated. Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving **RILOVIA 100/25** and **RILOVIA 200/50**. Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** is contraindicated in pulmonary arterial hypertension (PAH) patients (see section 4.3 and 4.5).

Tadalafil:

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

Vardenafil:

Use vardenafil with caution at reduced doses of no more than 2,5 mg every 72 hours with increased monitoring for adverse events.

Herbal medicines:

Patients on **RILOVIA 100/25** and **RILOVIA 200/50** should not use medicines 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 **RILOVIA 100/25** and **RILOVIA 200/50** with lovastatin or simvastatin is contra-indicated (see section 4.3).Caution should be exercised if HIV protease inhibitors, including **RILOVIA 100/25** and **RILOVIA 200/50**, 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 **RILOVIA 100/25** and **RILOVIA 200/50** and tipranavir with low dose ritonavir is therefore not recommended.

Liver disease:

The safety and efficacy of **RILOVIA 100/25** and **RILOVIA 200/50** have not been established in patients with significant underlying liver disorders. **RILOVIA 100/25** and **RILOVIA 200/50** are 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 events. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicines.

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.

Renal disease:

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 haemodialysis or peritoneal dialysis.

Resistance/Cross-Resistance:

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of **RILOVIA 100/25** and **RILOVIA 200/50** therapy 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 **RILOVIA 100/25** and **RILOVIA 200/50**. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors such as **RILOVIA 100/25** and **RILOVIA 200/50** was continued or reintroduced if treatment had been discontinued. Neither a causal relationship nor a mechanism of action between protease inhibitor therapy and these events has been established. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Lipid elevations:

Treatment with **RILOVIA 100/25** and **RILOVIA 200/50** may result in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing is to be performed prior to initiating **RILOVIA 100/25** and **RILOVIA 200/50** 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.
See section 4.5 for additional information on potential medicine interactions with **RILOVIA 100/25** and **RILOVIA 200/50** and HMG-CoA reductase inhibitors.

Pancreatitis:

Cases of pancreatitis have been reported in patients receiving lopinavir/ritonavir such as contained in **RILOVIA 100/25** and **RILOVIA 200/50** tablets, including those who developed hypertriglyceridaemia. In some cases fatalities have been observed. 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, and patients with a history of pancreatitis may be at increased risk for recurrence during **RILOVIA 100/25** and **RILOVIA 200/50** therapy. 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 **RILOVIA 100/25** and **RILOVIA 200/50** therapy should be suspended if a diagnosis of pancreatitis is made.

Diabetes Mellitus/Hyperglycaemia:

New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors such as **RILOVIA 100/25** and **RILOVIA 200/50**. 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 **RILOVIA 100/25** and **RILOVIA 200/50** therapy

and these events has not been established. Consideration should be given to the monitoring of blood glucose.

Fat redistribution and metabolic disorders:

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients. These may manifest as redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement ('buffalo hump'), peripheral wasting, facial wasting, breast enlargement and 'Cushingoid' appearance. The long-term consequences of these events are unknown. Knowledge about the mechanism is incomplete.

A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine 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, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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.

Opportunistic infections:

Patients receiving **RILOVIA 100/25** and **RILOVIA 200/50** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should

remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

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 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:

Lopinavir and ritonavir such as in **RILOVIA 100/25** and **RILOVIA 200/50** have been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd 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. **RILOVIA 100/25** and **RILOVIA 200/50** should be used with caution in such patients.

The risk of HIV transmission to others:

RILOVIA 100/25 and **RILOVIA 200/50** are 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. Patients taking **RILOVIA 100/25** and **RILOVIA 200/50** may still develop infections or other illnesses associated with HIV disease and AIDS.

Use in the elderly

Clinical studies of lopinavir/ritonavir such as contained in **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** in elderly patients reflecting

the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy.

Excipient information

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

RILOVIA 100/25 and **RILOVIA 200/50** is a potent inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50**. Medicines that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in the TABLE under **CONTRAINDICATIONS** (see section 4.3).

RILOVIA 100/25 and **RILOVIA 200/50** is metabolised by CYP3A. Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** and medicines that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect. Although not noted with concurrent ketoconazole, co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** 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 RILOVIA 100/25 and RILOVIA 200/50. The healthcare provider should consult appropriate references for comprehensive information.

ANTI-HIV MEDICINES

Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs):

Stavudine and lamivudine:

No change in the pharmacokinetics of lopinavir was observed when **RILOVIA 100/25** and **RILOVIA 200/50** tablets were given alone or in combination with stavudine and lamivudine in clinical studies.

Didanosine:

It is recommended that didanosine be administered on an empty stomach; therefore, didanosine may be co-administered with **RILOVIA 100/25** and **RILOVIA 200/50** without food.

Zidovudine and abacavir:

RILOVIA 100/25 and **RILOVIA 200/50** induce glucuronidation, therefore **RILOVIA 100/25** and **RILOVIA 200/50** have the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Tenofovir:

When tenofovir disoproxil fumarate was co-administered with **RILOVIA 100/25** and **RILOVIA 200/50** tablets, tenofovir concentrations were increased by approximately 30 % with no changes noted in lopinavir or ritonavir concentrations. Higher tenofovir concentrations could potentiate tenofovir associated adverse events, including renal disorders.

All anti-HIV medicines:

Increased creatinine phosphokinase (CPK), myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitor's such as **RILOVIA 100/25** and **RILOVIA 200/50,** particularly in combination with NRTIs.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Efavirenz:

In a study performed in healthy volunteers to explore the interaction between **RILOVIA 100/25** and **RILOVIA 200/50** tablets (400/100 mg twice daily) and efavirenz (600 mg once daily), efavirenz has been shown to decrease the lopinavir concentrations by 30 – 40 %. When **RILOVIA 100/25** and **RILOVIA 200/50** dosages were increased to 500/125 mg twice daily during co-administration of efavirenz 600 mg once daily in healthy volunteers, lopinavir pharmacokinetic parameters were similar to those obtained with **RILOVIA 100/25** and **RILOVIA 200/50** tablets 400/100 mg twice daily administered alone. Therefore, the **RILOVIA 100/25** and **RILOVIA 200/50** dosage should be increased to 500/125 mg twice daily when co-administered with efavirenz 600 mg once daily. Increasing the dose of **RILOVIA 100/25** and **RILOVIA 200/50** to 600/150 mg twice daily co-administered with efavirenz significantly increased lopinavir plasma concentrations by approximately 36 % and ritonavir concentrations by approximately 56 % to 92 % compared to **RILOVIA 100/25** and **RILOVIA 200/50** 400/100 mg twice daily without efavirenz.
NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with **RILOVIA 100/25** and **RILOVIA 200/50**. **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required. Refer to the rilpivirine prescribing professional information.

Nevirapine:

Similar pharmacokinetic interactions are expected for the co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** with the NNRTI nevirapine and with the protease inhibitors nelfinavir and amprenavir. That is decreases in the concentration of lopinavir and increases in the concentrations of nevirapine, nelfinavir and amprenavir. The same recommendations for monitoring apply in these cases of co-administration.

Co-administration with other HIV protease inhibitors (PIs):

Amprenavir:

RILOVIA 100/25 and **RILOVIA 200/50** is expected to increase concentrations of amprenavir. Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** and amprenavir result in decreased concentrations of lopinavir. The dose of **RILOVIA 100/25** and **RILOVIA 200/50** may need to be increased during co-administration of amprenavir, particularly in patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir. **RILOVIA 100/25** and **RILOVIA 200/50** should not be administered once daily in combination with amprenavir.

Fosamprenavir:

Co-administration of standard doses of **RILOVIA 100/25** and **RILOVIA 200/50** with fosamprenavir results in a significant reduction in amprenavir concentrations. 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. Therefore, concomitant administration of these medicines is not recommended.

Indinavir:

Indinavir 600 mg twice daily in combination with **RILOVIA 100/25** and **RILOVIA 200/50** tablets produced similar indinavir AUC, higher C_{min} (by 3,5-fold) and lower C_{max} relative to indinavir 800 mg three times daily alone.

Nelfinavir:

RILOVIA 100/25 and **RILOVIA 200/50** are expected to increase concentrations of nelfinavir and increase the M8 metabolite of nelfinavir (nelfinavir 1000 mg twice daily plus **RILOVIA 100/25** and **RILOVIA 200/50** produced similar AUC, similar C_{max}, increased C_{min} relative to nelfinavir 1250 mg twice daily). Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** and nelfinavir resulted in decreased concentrations of lopinavir. **RILOVIA 100/25** and **RILOVIA 200/50** should not be administered once daily in combination with nelfinavir.

Saquinavir:

Saquinavir 800 mg twice daily co-administered with **RILOVIA 100/25** and **RILOVIA 200/50** produced an increase of saquinavir AUC by 9,6-fold relative to saquinavir 1200 mg three times daily given alone.

Ritonavir:

RILOVIA 100/25 and **RILOVIA 200/50** tablets co-administered with an additional 100 mg ritonavir twice daily resulted in an increase of lopinavir AUC and C_{min} of 33 % and 64 %, respectively, as compared to **RILOVIA 100/25** and **RILOVIA 200/50** tablets alone.

Hepatitis C direct acting antivirals

Boceprevir:

Concomitant administration of boceprevir and **RILOVIA 100/25** and **RILOVIA 200/50** resulted in reduced boceprevir and lopinavir steady-state exposure. It is not recommended to co-administer **RILOVIA 100/25** and **RILOVIA 200/50** and boceprevir.

Glecaprevir/pibrentasvir:

Concomitant administration of glecaprevir/pibrentasvir and **RILOVIA 100/25** and **RILOVIA 200/50** is not recommended due to an increased risk of ALT elevations associated with increased GLE exposure.

Ombitasvir/paritaprevir/ritonavir and dasabuvir:

Concentrations of ombitasvir, paritaprevir, and ritonavir may be increased when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50** therefore, co-administration is not recommended.

Simeprevir:

Concomitant use of **RILOVIA 100/25** and **RILOVIA 200/50** and simeprevir may result in increased plasma concentrations of simeprevir. It is not recommended to co-administer **RILOVIA 100/25** and **RILOVIA 200/50**, and simeprevir.

Sofosbuvir/velpatasvir/voxilaprevir:

Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and **RILOVIA 100/25** and **RILOVIA 200/50** is not recommended due to the potential for increased toxicity, which may negatively impact compliance.

Telaprevir:

Concomitant administration of telaprevir and **RILOVIA 100/25** and **RILOVIA 200/50** resulted in reduced telaprevir steady-state exposure, while the lopinavir steady state exposure was not affected.

HIV CCR5 – antagonist

Maraviroc: Concurrent administration of maraviroc with **RILOVIA 100/25** and **RILOVIA 200/50** 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: **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50**.

Antidysrhythmics

Amiodarone, bepridil, dronedarone, systemic lidocaine, lignocaine (lidnocaine) and quinidine:

Concentrations may be increased when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50**. Caution is warranted and therapeutic concentration monitoring is recommended when available (see **CONTRAINDICATIONS**).

Digoxin:

Plasma concentrations of digoxin may be increased when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50**. Caution is warranted and therapeutic monitoring of digoxin concentrations, if available, is recommended in case of co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** and digoxin. Particular caution should be used when prescribing **RILOVIA 100/25** and **RILOVIA 200/50** in patients taking digoxin as the acute inhibitory effect of ritonavir on P-gp is expected to significantly increase digoxin levels.

Dihydropyridine calcium channel blockers

(e.g. felodipine, nifedipine, nicardipine):

May have their serum concentrations increased by **RILOVIA 100/25** and **RILOVIA 200/50**.

Anticoagulants

Warfarin: Warfarin concentrations may be affected when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50**. 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.

Medicines that prolong QT interval

Particular caution must be used when prescribing **RILOVIA 100/25** and **RILOVIA 200/50** and medicines known to induce QT interval prolongation such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. **RILOVIA 100/25** and **RILOVIA 200/50** tablets could increase concentrations of the co-administered medicines and this may result in an increase of their associated cardiac adverse events. Cardiac events have been reported with **RILOVIA 100/25** and **RILOVIA**

200/50 tablets in preclinical studies; therefore, the potential cardiac effects of **RILOVIA 100/25** and **RILOVIA 200/50** cannot be currently ruled out.

Anticancer medicines

Abemaciclib, apalutamide, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vincristine, vinblastine:

These medicines may have their serum concentrations increased when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50,** resulting in the potential for increased adverse events usually associated with these anticancer medicines, 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 tumour lysis syndrome. Co-administration of encorafenib or ivosidenib with **RILOVIA 100/25** and **RILOVIA 200/50** 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.

Co-administration of apalutamide is contraindicated with **RILOVIA 100/25** and **RILOVIA 200/50** since apalutamide may decrease exposure of **RILOVIA 100/25** and **RILOVIA 200/50** with potential loss of virologic response. In addition, co-administration of apalutamide and **RILOVIA 100/25** and **RILOVIA 200/50** may lead to increased exposure of apalutamide resulting in increased potential for adverse events including seizure.

Anticonvulsants

Phenobarbital, phenytoin, carbamazepine:

These medicines will induce CYP3A4 and may decrease lopinavir concentrations. **RILOVIA 100/25** and **RILOVIA 200/50** should not be administered once daily in combination with phenobarbital, phenytoin or carbamazepine.

In addition, co-administration of phenytoin and **RILOVIA 100/25** and **RILOVIA 200/50** resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with **RILOVIA 100/25** and **RILOVIA 200/50**.

Lamotrigine and valproate: Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments.

Antidepressants:

Bupropion:

In healthy volunteers, the AUC and C_{max} of bupropion and of its active metabolite, hydroxybupropion, were decreased by about 50 % when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50** 400/100 mg twice daily at steady-state. Therefore, if the co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** 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.

Trazodone:

In a pharmacokinetic study performed in healthy volunteers, concomitant use of low dose ritonavir (200 mg twice daily) with a single dose of trazodone led to an increase in plasma concentrations of trazodone (AUC increased by 2,4-fold). Adverse events of nausea, dizziness, hypotension and syncope were observed following co-administration of trazodone and ritonavir in a clinical study. **RILOVIA 100/25** and **RILOVIA 200/50** should be used with caution and a lower dose of trazodone should be considered.

Midazolam:

Midazolam is extensively metabolised by CYP3A4. Co-administration with **RILOVIA 100/25** and **RILOVIA 200/50** may cause a large increase in the concentration of midazolam. A phenotyping cocktail study in 14 healthy volunteers showed an increase of AUC by about 13-fold with oral midazolam and an increase by about 4-fold with parenteral midazolam. Therefore, **RILOVIA 100/25** and **RILOVIA 200/50** tablets co-administered with orally administered midazolam are contraindicated

and caution should be exercised with co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** and parenteral midazolam. If **RILOVIA 100/25** and **RILOVIA 200/50** tablets are 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 (see section 4.3).

HMG-CoA reductase inhibitors

Lovastatin and Simvastatin: HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50**. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicines with **RILOVIA 100/25** and **RILOVIA 200/50** are contraindicated (see section 4.3).

Atorvastatin: Atorvastatin is less dependent on CYP3A for metabolism. When atorvastatin was given concurrently with **RILOVIA 100/25** and **RILOVIA 200/50** tablets, a mean 4,7-fold and 5,9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with **RILOVIA 100/25** and **RILOVIA 200/50**, the lowest possible dose of atorvastatin should be administered.

Pravastatin and Fluvastatin: Results from an interaction study with **RILOVIA 100/25** and **RILOVIA 200/50** tablets and pravastatin revealed no clinically significant interaction. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4 and interactions are not expected with **RILOVIA 100/25** and **RILOVIA 200/50**. 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).

Corticosteroids

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

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

Fluticasone propionate (interaction with ritonavir):

In a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for seven days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86 % (90 % confidence interval 82 − 89 %). 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 metabolised via the P450 3A pathway e.g. budesonide. Consequently, concomitant administration of **RILOVIA 100/25** and **RILOVIA 200/50** 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. The effect of high fluticasone systemic exposure on ritonavir plasma levels is yet unknown.

PDE5 inhibitors

Phosphodiesterase inhibitors which are dependent on CYP3A4 metabolism, such as tadalafil and sildenafil, are expected to result in an approximately 2-fold and 11-fold increase in AUC respectively, when co-administered with ritonavir containing regimens including **RILOVIA 100/25** and **RILOVIA 200/50** and may result in an increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection. Particular caution must be used when prescribing sildenafil or tadalafil in patients receiving **RILOVIA 100/25** and **RILOVIA 200/50** with increased monitoring for adverse events. Doses of no more than 25 mg sildenafil every 48 hours and 10 mg tadalafil every 72 hours. Co-administration of vardenafil with ritonavir containing regimens including **RILOVIA 100/25** and **RILOVIA 200/50** is expected to result in 49-fold increase in vardenafil

AUC. The use of vardenafil with **RILOVIA 100/25** and **RILOVIA 200/50** is contraindicated.

Concomitant use of sildenafil with **RILOVIA 100/25** and **RILOVIA 200/50** is contraindicated in pulmonary arterial hypertension (PAH) patients.

Avanafil: Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50** 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: Co-administration of fostamatinib with **RILOVIA 100/25** and **RILOVIA 200/50** could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia.

Immunosuppressants

Cyclosporin, sirolimus (rapamycin) and tacrolimus: Concentrations of these medicines may be increased when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50**. More frequent therapeutic concentration monitoring is recommended until plasma levels of these medicines have been stabilised.

Antifungals

Ketoconazole and itraconazole: Ketoconazole and itraconazole may have their serum concentrations increased by **RILOVIA 100/25** and **RILOVIA 200/50**. High doses of ketoconazole and itraconazole (> 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, coadministration of **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50**. Life-threatening and fatal medicine interactions have been reported in patients treated with colchicine and ritonavir. Concomitant administration 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 section 4.4).

Anti-infectives

Clarithromycin: Moderate increases in clarithromycin AUC are expected when co-administered with **RILOVIA 100/25** and **RILOVIA 200/50**. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered.

Methadone

RILOVIA 100/25 and **RILOVIA 200/50** tablets were demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Oral Contraceptives or Patch Contraceptives

Levels of ethinyl oestradiol were decreased when oestrogen-based oral contraceptives were co-administered with **RILOVIA 100/25** and **RILOVIA 200/50** tablets. In case of co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** with contraceptives containing ethinyl oestradiol (whatever the contraceptive formulation e.g. oral or patch), alternative or additional contraceptive measures are to be used.

Vasodilating medicines

Bosentan: Co-administration of bosentan and **RILOVIA 100/25** and **RILOVIA 200/50** 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.

Anti-mycobacterials

Rifabutin:

When rifabutin and **RILOVIA 100/25** and **RILOVIA 200/50** tablets were co-administered for 10 days, rifabutin (parent substance and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3,5- and 5,7-fold, respectively. On the basis of these data, a rifabutin dose reduction of 75 % (i.e. 150 mg every other day or 3 times per week) is recommended when administered with **RILOVIA 100/25** and **RILOVIA 200/50**. Further reduction of rifabutin dose may be necessary.

Rifampicin:

Co-administration of **RILOVIA 100/25** and **RILOVIA 200/50** with rifampicin is not recommended. Rifampicin administered with **RILOVIA 100/25** and **RILOVIA 200/50** caused large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect and possible resistance to **RILOVIA 100/25** and **RILOVIA 200/50** or to the class of protease inhibitors or other co-administered antivirals. 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, **RILOVIA 100/25** and **RILOVIA 200/50** should be initiated at standard dose for approximately 10 days prior to addition of rifampicin. **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50**, 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 **RILOVIA 100/25** and **RILOVIA 200/50** 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 **RILOVIA 100/25** and **RILOVIA 200/50**. Increases in atovaquone doses may be necessary.

Antipsychotics

Quetiapine: Due to CYP3A inhibition by **RILOVIA 100/25** and **RILOVIA 200/50,** concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities.

Herbal medicines

St John's Wort: Serum levels of **RILOVIA 100/25** and **RILOVIA 200/50** can be reduced with resultant loss of therapeutic effect and development of resistance by concomitant use of the herbal medicine St John's Wort (*Hypericum perforatum).* This is due to the induction of metabolising enzymes by St John's Wort. Herbal medicines containing St. John's Wort should therefore not be combined with **RILOVIA 100/25** and **RILOVIA 200/50** (see section 4.3)

Clinically Significant Medicine Interactions Not Expected

Acid reducing medicines (omeprazole, ranitidine):

Medicine interaction studies reveal no clinically significant interaction is expected when **RILOVIA 100/25** and **RILOVIA 200/50** are co-administered with desipramine (CYP2D6 probe), omeprazole or with ranitidine.

General:

Based on known metabolic profiles, clinically significant interactions are not expected between **RILOVIA 100/25** and **RILOVIA 200/50** tablets and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole in patients with normal renal and hepatic function.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **RILOVIA 100/25** and **RILOVIA 200/50** 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

Studies in rats revealed that lopinavir is excreted in the milk. It is not known whether **RILOVIA 100/25** and **RILOVIA 200/50** are excreted in human milk.

HIV-infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV and the potential for serious adverse reactions in breastfeeding infants, if they are receiving **RILOVIA 100/25** and **RILOVIA 200/50**.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be informed that nausea and dizziness have been reported during treatment with **RILOVIA 100/25** and **RILOVIA 200/50**.

4.8 Undesirable effects

The following side effects of moderate to severe intensity with possible or probable relationship to **RILOVIA 100/25** and **RILOVIA 200/50** have been reported. The side effects are displayed by system organ class.

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.

Tabulated list of adverse reactions

Undesirable Effects in Clinical Studies in Adult Patients		
Infections and infestations	Less frequent	Otitis media, bronchitis, sinusitis, furunculosis, bacterial infection, viral infection, upper & lower respiratory tract infection, skin infections (including cellulitis, folliculitis and furuncle)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Less frequent	Skin benign neoplasm, cyst
Blood and lymphatic system disorders	Frequent	Anaemia, leucopenia, lymphadenopathy, neutropenia
Immune system disorders	Frequent	Hypersensitivity (including urticaria and angioedema)
	Less frequent	Immune reactivation syndrome
Endocrine disorders	Less frequent	Hypogonadism male, Cushing syndrome, hypothyroidism

Metabolic and nutrition disorders	Frequent	hypercholesterolaemia, hypertriglyceridaemia, lactic acidosis, blood glucose disorders including diabetes mellitus, hyperglycaemia, decreased appetite
	Less frequent	Avitaminosis, dehydration, oedema, increased appetite, obesity, anorexia
Psychiatric disorders	Frequent	Insomnia, anxiety
	Less frequent	Abnormal dreams, agitation, confusion, depression, dyskinesia, emotional lability, decreased libido, nervousness, abnormal thinking
Nervous system disorders	Frequent	Headache (including migraine), neuropathy including (peripheral neuropathy), dizziness, paraesthesia
	Less frequent	Amnesia, ataxia, encephalopathy, facial paralysis, hypertonia, peripheral neuritis, somnolence, tremor, taste loss (ageusia), taste perversion (dysgeusia), extrapyramidal syndrome, cerebrovascular accident (CVA), convulsion
Eye disorders	Less frequent	Abnormal vision/visual

		impairment, eye disorder
Ear and labyrinth disorders	Less frequent	Tinnitus, vertigo
Cardiac disorders	Less frequent	Atherosclerosis, angina pectoris, atrioventricular block, tricuspid valve incompetence, palpitation, lung oedema, myocardial infarction [1]
Vascular disorders	Frequent	Hypertension
	Less frequent	Thrombophlebitis, vasculitis, varicose vein, deep thrombophlebitis, vascular disorder, vasodilation
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, rhinitis, increased cough
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting, colitis abdominal pain (upper and lower), abnormal stools, dyspepsia, flatulence, gastrointestinal disorder, pancreatitis, gastroesophageal reflux disease, gastroenteritis, haemorrhoids
	Less frequent	Enlarged/distended abdomen, constipation, dry mouth, dysphagia, enterocolitis, eructation, oesophagitis, faecal incontinence, gastritis,

		haemorrhagic colitis, mouth ulcerations, sialadenitis, stomatitis, ulcerative stomatitis, periodontitis, gastrointestinal haemorrhage (including gastrointestinal ulcer), duodenitis, gastric ulcer, rectal haemorrhage
Hepato-biliary disorders	Frequent	Hepatitis (including AST, ALT and GGT increases)
	Less frequent	Cholecystitis, hepatomegaly, hepatic steatosis (liver fatty deposit), liver tenderness, cholangitis, hyperbilirubinaemia, jaundice
Skin and subcutaneous tissue disorders	Frequent	Rash (including maculopapular rash), dermatitis/rash (including eczema and seborrheic dermatitis), lipodystrophy, acne, night sweats, pruritus
	Less frequent	Alopecia, dry skin, exfoliative dermatitis, nail disorder, seborrhoea, skin discolouration, skin ulcer, face oedema, skin striae, capillaritis, Stevens-johnson syndrome, erythema multiforme

Musculoskeletal and connective tissue disorders	Frequent	Myalgia, musculoskeletal pain (including arthralgia and back pain), muscle disorders (such as weakness and spasms)
	Less frequent	Arthrosis, joint disorder, rhabdomyolysis, osteonecrosis
Renal and urinary disorders	Less frequent	Kidney calculus, urine abnormality, albuminuria, hypercalcinuria, nephritis, hyperuricaemia, creatinine clearance decreased, haematuria
Reproductive system and breast disorders	Frequent	Erectile dysfunction, menstrual disorders (amenorrhoea, menorrhagia)
	Less frequent	Abnormal ejaculation, breast enlargement, gynaecomastia, impotence
General disorders and administration site conditions	Frequent	Fatigue (including asthenia), pain
	Less frequent	Chest pain, substernal chest pain, chills, fever, flu syndrome, malaise, peripheral oedema

Investigations	Frequent	Increased triglycerides, increased total cholesterol, increased GGT, increased glucose, increased amylase, increased AST, increased ALT, abnormal liver function tests
	Less frequent	Decreased glucose tolerance, weight gain, weight loss, increased bilirubin, hormone level altered, lab test abnormal

[1] This event had a fatal outcome.

Paediatric patients:

In children BSA > 1,4 m [2], the nature of the safety profile is similar to that seen in adults.

Undesirable Effects in Paediatric Patients		
Infections and infestations	Frequent	Viral infection
Nervous system disorders	Frequent	Taste perversion
Gastrointestinal disorders	Frequent	Constipation, vomiting, pancreatitis
Hepatobiliary disorders	Frequent	Hepatomegaly
Skin and subcutaneous tissue disorders	Frequent	Rash, dry skin
General disorders and administration site conditions	Frequent	Fever

Investigations	Frequent	Increased activated partial thromboplastin time, decreased haemoglobin, decreased platelets, increased sodium, increased potassium, increased calcium, increased bilirubin, increased ALT, increased AST, increased total cholesterol, increased amylase, increased uric acid, decreased sodium, decreased potassium, decreased calcium, decreased neutrophils

The most common adverse reaction associated with **RILOVIA 100/25** and **RILOVIA 200/50** therapy was diarrhoea and was generally of mild to moderate severity. Discontinuation due to adverse reactions was 4,5 % (naïve patients) and 9 % (experienced patients) over a 48 week period.

It is important to note that cases of pancreatitis have been reported in patients receiving **RILOVIA 100/25** and **RILOVIA 200/50**, including those who developed hypertriglyceridaemia. Furthermore, rare increases in PR interval have been reported during **RILOVIA 100/25** and **RILOVIA 200/50** therapy.

Increased 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 hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

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.

Post marketing experience:

Hepatobiliary disorders: Hepatitis, and rarely jaundice, have been reported in patients on lopinavir and ritonavir tablets therapy such as in **RILOVIA 100/25** and **RILOVIA 200/50**, in the presence or absence of identifiable risk factors for hepatitis.

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

Cardiac disorders: Bradydysrhythmia has been reported.

Musculoskeletal and connective tissue disorders: 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). *Renal and urinary disorders:* Nephrolithiasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is limited human experience of overdose with **RILOVIA 100/25** and **RILOVIA 200/50**.

There is no specific antidote for overdose with **RILOVIA 100/25** and **RILOVIA 200/50**. Treatment of overdose with **RILOVIA 100/25** and **RILOVIA 200/50** 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 medicine is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed medicine. Since **RILOVIA 100/25** and **RILOVIA 200/50** are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antiviral agents

Pharmaco-therapeutic group: antivirals for systemic use, antivirals for treatment of HIV infections, combinations, ATC code: J05AR10

Mechanism of action:

Lopinavir/ritonavir tablets are a co-formulation of lopinavir and ritonavir. As co-formulated in lopinavir/ritonavir tablets, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. Lopinavir provides the antiviral activity of **RILOVIA 100/25** and **RILOVIA 200/50** tablets. 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.

Antiviral activity in vitro:

The *in vitro* antiviral activity of lopinavir against laboratory and clinical HIV strains was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean IC_{50} of lopinavir against five different HIV-1 laboratory strains ranged from 10 – 27 nM. In the presence of 50 % human serum, the mean IC_{50} of lopinavir against these live laboratory strains ranged from 68 – 289 nM.

Resistance:

In vitro selection of resistance:

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. HIV-1 has been passaged *in vitro* with lopinavir alone and with lopinavir plus ritonavir at concentration ratios representing the range of plasma concentration ratios observed during lopinavir and ritonavir therapy. Genotypic and phenotypic analysis of viruses selected in these passages suggests that the presence of ritonavir, at these concentration ratios, does not measurably influence the selection of lopinavir-resistant viruses.

Cross-resistance:

Activity of other protease inhibitors against isolates that developed incremental resistance to lopinavir after lopinavir/ritonavir tablets therapy in protease inhibitor experienced patients: The presence of cross-resistance to other protease inhibitors was analysed in 18 rebound isolates that had demonstrated evolution of resistance to lopinavir during 3 Phase II and one Phase III studies of lopinavir/ritonavir tablets in protease inhibitor-experienced patients. The median fold IC_{50} of lopinavir for these 18 isolates at baseline and rebound was 6,9- and 63-fold, respectively, compared to wild type virus. In general, rebound isolates either retained (if cross-resistant at baseline) or developed significant cross-resistance to indinavir, saquinavir and atazanavir. Modest decreases in amprenavir activity were noted with a median increase of IC_{50} from 3,7- to 8-fold in the baseline and rebound isolates, respectively. Isolates retained susceptibility to tipranavir with a median increase of IC_{50} in baseline and rebound isolates of 1,9- and 1,8–fold, respectively, compared to wild type virus.

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

Absorption:

Multiple dosing with 400/100 mg lopinavir/ritonavir tablets twice daily for 3 to 4 weeks and without meal restriction produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9,6 ± 4,4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5,5 ± 4,0 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 82,8 ± 44,5 µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of food on oral absorption*:*

Administration of a single 400/100 mg dose of lopinavir/ritonavir tablets under fed conditions (high fat, 872 kcal, 56 % from fat) compared to 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.

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

Metabolism:

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

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 faeces, respectively, after 8 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 effective (peak to trough) half-life of lopinavir over a 12 hour dosing interval averaged 5 − 6 hours, and the apparent clearance (CL/F) of lopinavir is 6 to 7 l/h.

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 ± 3,5 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 the 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 limit) differences in QTcF from placebo were 3,6 (6,3) and 13,1(15,8) for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily LPV/r, respectively. The induced QRS interval prolongation from 6 ms to 9,5 ms with high dose lopinavir/ritonavir (800/200 mg twice daily) contributes to QT prolongation. The two regimens resulted in exposures on Day 3 which were approximately 1,5 and 3-fold higher than those observed with recommended once daily or twice daily LPV/r 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. The mean changes from baseline in PR interval ranged from 11,6 ms to 24,4 ms in the 12 hour interval post dose. Maximum PR interval was 286 msec and no second or third degree heart block was observed.

Special Populations

Paediatrics:

There are limited pharmacokinetic data in children below 2 years of age. The pharmacokinetics of lopinavir/ritonavir oral solution 300/75 mg/m^2 twice daily and 230/57,5 mg/m^2 twice daily have been studied in a total of 53 paediatric patients, ranging in age from 6 months to 12 years. The lopinavir mean steady state AUC, C_{max}, and C_{min} were 72,6 ± 31,1 µg•h/ml, 8,2 ± 2,9 µg/ml and 3,4 ± 2,1 µg/ml, respectively after lopinavir/ritonavir oral solution 230/57,5 mg/m^2 twice daily without nevirapine (n=12), and were 85,8 ± 36,9 µg•h/ml, 10,0 ± 3,3 µg/ml and 3,6 ± 3,5 µg/ml, respectively after 300/75 mg/m^2 twice daily with nevirapine (n=12). The 230/57,5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen without nevirapine.

Gender, Race and Age:

Lopinavir/ritonavir tablets pharmacokinetics have not been studied in the elderly. No age or gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Renal Insufficiency:

Lopinavir/ritonavir tablets 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 Insufficiency:

Lopinavir is principally metabolised and eliminated by the liver. The steady state pharmacokinetic parameters of lopinavir in HIV-infected patients with mild to moderate hepatic impairment were compared with those of HIV-infected patients with normal hepatic function in a multiple dose study with lopinavir/ritonavir 400/100 mg twice daily. A limited increase in total lopinavir concentrations of approximately 30 % and 20 % in C_{max} has been observed. Additionally, the plasma protein binding of lopinavir was lower in both mild and moderate hepatic impairment compared to controls (99,09 vs

99,31 % respectively). Lopinavir/ritonavir has not been studied in patients with severe hepatic impairment (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium stearyl fumarate, colloidal silicon dioxide, copovidone, sorbitan monolaurate, film-coat (hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, iron oxide yellow, talc, polyethylene glycol 3350, polysorbate 80, colloidal anhydrous silica).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

RILOVIA 100/25: 36 months

RILOVIA 200/50: 36 months

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original container.

Do not remove from the carton until required for use. Keep the bottles tightly closed.

6.5 Nature and contents of container

RILOVIA 100/25 film-coated tablets will be packed in a round, white and opaque 250 ml HDPE container (Pill jar) (marketable pack) with a white, opaque, tamper-evident polypropylene (PP) closure containing an inbuilt desiccant packed with or without a carton in pack sizes of 56’s, 60’s 112’s and 120’s*.

RILOVIA 100/25 film-coated tablets will be packed in an HDPE bottle pack (marketable pack) comprises of round, wide mouth white HDPE bottle with white opaque polypropylene (PP) screw closure containing desiccant packed in pack sizes of 56’s, 60’s, 112’s and 120’s.

RILOVIA 100/25 film-coated tablets will be packed in a blue HDPE bottle pack comprising of blue opaque HDPE bottle with blue opaque polypropylene (PP) screw closure with aluminium inductions sealing wad with or without desiccant in pack sizes of 60's and 120's.

RILOVIA 200/50 film-coated tablets will be packed in white opaque HDPE bottle with white opaque polypropylene (PP) tamper evident closure with inbuilt desiccant packed with or without a carton in pack sizes of 112's and 120's*.

RILOVIA 200/50 film-coated tablets will be packed in white opaque HDPE bottle with white opaque polypropylene (PP) child resistant closure with aluminium induction sealing wad. Separate desiccant is included in the final pack. Packed into a carton in pack size of 112's and 120's*.

RILOVIA 200/50 film-coated tablets will be packed in blue opaque HDPE bottle with blue opaque polypropylene (PP) screw closure with aluminium induction sealing wad without desiccant in pack sizes of 120's.

*Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street, Isando

Johannesburg, 1601,

Gauteng,

Republic of South Africa

8. REGISTRATION NUMBERS

RILOVIA 100/25: 45/20.2.8/0336

RILOVIA 200/50: 45/20.2.8/0111

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

20 January 2022

10. DATE OF REVISION OF THE TEXT

27 January 2025